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16. ABSTRACT

Tetrachloroethylene (PERC) is believed to exert its adverse effects upon humans via metabolism by the liver. Concern that PERC is likely to be a human carcinogen is based upon the evidence of the National Cancer Institute bioassay, in which PERC induced a statistically significant increase in the incidence of hepatocellular carcinomas in both sexes of B6C3F1 mice. Tetrachloroethylene has not been clearly demonstrated to cause point mutations in bacteria, but it may be genetically active in yeast.

The potential of PERC to produce adverse teratogenic or reproductive effects is, at present, undetermined. Of special concern is the observation that PERC is preferentially concentrated in maternal milk. Thus, nursing infants may represent a special risk group.

Both acute and chronic exposure levels have the potential to cause liver damage in humans. In animals, the lowest observable adverse effect level is 100 ppm. However, this may not be sufficiently protective of human health with regard to liver and kidney toxicity.

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HEALTH ASSESSMENT DOCUMENT FOR TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

Notice:

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

U.S. ENVIRONMENTAL PROTECTION AGENCY

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1.a

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PREFACE

The Office of Health and Environmental Assessment, in consultation with an Agency work group, has prepared this health assessment to serve as a "source document" for Agency-wide use. Originally the health assessment was developed for use by the Office of Air Quality Planning and Standards; however, at the request of the Agency Work Group on Solvents the assessment scope was expanded to address multimedia aspects. This assessment will help insure consistency in the Agency's consideration of the relevant scientific health data associated with tetrachloroethylene.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

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1. SUMMARY AND CONCLUSIONS

1.1 ENVIRONMENTAL SOURCES, FATE, AND LEVELS

Tetrachloroethylene (PERC), a colorless liquid of moderate volatility, has important commercial applications in the dry cleaning of fabrics and in the degreasing of fabricated metal parts.

Although it is a contaminant of water and a component in solid wastes, it is generally recognized as an atmospheric pollutant. It is so widely detected in ambient air that some investigators have termed it an "ubiquitous pollutant." Its physical properties would indicate that PERC present in water would be conveyed to the atmosphere by evaporation.

Tetrachloroethylene is relatively insoluble in water (150 mg/l) and has a vapor pressure of 0.19 pascals at 20°C. Its evaporative half-life in aqueous solution, as determined under laboratory conditions, has been estimated at about 30 minutes. In the natural aquatic environment its persistence would be expected to be considerably longer.

In the United States, PERC is produced primarily from the oxychlorination of 1,2-dichloroethane and chlorination of hydrocarbons. It has been estimated that 295,000 metric tons were produced in the United States in 1980. U.S. production generally is estimated to be about 45 percent of worldwide production. Tetrachloroethylene is released to ambient air as a result of evaporative losses during production, storage, and use. In the United States about 90 percent of production is emitted to the atmosphere.

In the troposphere (a region of the atmosphere extending to between 8 and 16 km above the earth's surface), PERC undergoes photochemical degradation. Phosgene, a potent respiratory toxicant, is an expected degradation product and is an identified contaminant of urban air. Although estimates of PERC's persistence in the troposphere varies, it exists in its original form for one year or less. As a result of chemical reaction with hydroxyl radicals in the troposphere, only a few percent of the amount of PERC released is estimated to be conveyed to higher regions of the atmosphere, e.g., the stratosphere.

Because of the reduced solar flux in winter and seasonal variations in hydroxyl concentration, PERC levels in ambient air are expected to be higher in winter than in summer. On a daily basis, PERC levels have been observed to fluctuate considerably; higher levels have been observed in morning and evening hours.

Tetrachloroethylene has been detected in the ambient air of numerous sites worldwide. The global average background level in ambient air (ground level) is about 26 ppt (0.176×10^{-3} mg/m^3). The estimated quantities inhaled by individuals in the general public range from a trace to about 1.5 mg/week depending on whether the individual lives in a rural or urban area. Levels detected in urban air typically have not exceeded 10 ppb (0.068 mg/m^3). The highest monitored level (during a 14 minute sampling period) was 58 ppb (0.394 mg/m^3), measured at a waste disposal site.

Levels of PERC in water are generally about 1 μg/l, based on monitoring studies of the drinking waters of various U.S. cities. Contamination of well water is an area of concern. The highest monitored level in well water is 375 μg/l. Well water contamination by PERC may be the result of PERC disposal at unregulated sites. There is very limited information on the behavior of PERC in soil; PERC can be envisioned to leach through soils of low (< 0.1%) organic carbon content. The amount of PERC adsorbed to soils is dependent upon PERC's partition coefficient, the organic carbon content of the soil, and the concentration of PERC in the liquid phase.

Tetrachloroethylene in ambient air is sampled and analyzed by a variety of procedures. Where very low levels (sub ppb) exist, sampling is accomplished by adsorption onto activated charcoal, followed by desorption with carbon disulfide. This has been used in field studies to collect 24-hour samples. Other investigators have preconcentrated air samples prior to analysis. Tetrachloroethylene is generally analyzed by gas chromatography coupled with either mass spectrometry or electron capture detection. Both systems have a detection limit on the order of a few parts per trillion or less. Using a concentration technique coupled with gas chromatography and electron capture detection, investigators have reported a detection limit of 0.2 ppt for 500 ml aliquots of ambient air samples.

A variety of techniques and methods are commonly used to sample and quantitate trace levels of PERC in water samples. Gas purging and trapping and headspace analysis are frequently used techniques. Detection limits are on the order of 1 μg/l when analysis is accomplished by gas chromatography coupled with mass spectrometry.

1.2 COMPOUND DISTRIBUTION AND RELATED PHARMACOKINETICS

Inhalation is the principal route by which PERC enters the body. Ingestion of drinking water is a secondary, though important, source of exposure. During inhalation, PERC is absorbed by the blood and distributed throughout the body.

Controlled studies with human volunteers has shown that between 3 to 4 hours is required to reach pulmonary steady-state conditions. Upon repeated exposure to levels in the range of 100 ppm (678 mg/m^3), absorption and lung clearance decreased. Physical activity increases the uptake of PERC. At levels approaching those found or expected in ambient air, the time required to reach steady-state conditions may be considerably longer such that absorption by the lungs persists.

Because PERC is lipophilic (its fat/blood partition coefficient = 90) it is likely to be stored in lipid-rich tissues, such as adipose and brain tissue.

Continuous exposure to PERC at levels generally found in ambient air and water is likely to result in accumulation of PERC in the body, particularly since release from adipose tissue is slow. This retention results in a slow elimination of PERC from the body; two weeks or more may be necessary to remove PERC completely from the body upon cessation of exposure.

Tetrachloroethylene is believed to exert its effects upon humans via its metabolism by the liver. There is evidence, from animal studies, that PERC is metabolized by the cytochrome P-450 mixed function oxidases in the liver and is converted to an activated intermediate, tetrachloroethylene epoxide. This epoxide has great propensity to interact with nucleophilic sites thus possibly resulting in alterations of cellular metabolism. Such interaction in the liver is believed responsible for the hepatocarcinogenic potential of PERC.

In vitro studies have shown that PERC binds to cytochrome P-450 and may act to uncouple electron transfer. Phenobarbital, a cytochrome P-450 inducer administered *in vivo*, did not alter the *in vitro* binding constant associated with PERC and induced cytochrome P-450.

Both controlled and occupational exposures of humans to PERC indicate that the principal urinary excretion product of PERC metabolism is trichloroacetic acid. Controlled studies with humans have demonstrated that urinary trichloroacetic acid represents 2 percent or less of the amount of PERC absorbed. Most PERC inhaled is excreted via the lungs in unchanged form. Trichloroethanol is a minor urinary excretion product but may be of toxicologic importance since it may have neuro- and cardiotoxic potential.

1.3 EFFECTS UPON HUMANS

1.3.1 Carcinogenicity, Mutagenicity and Teratogenicity and Other Reproductive Effects

Concern that PERC is a potential human carcinogen is based upon the evidence of the National Cancer Institute (NCI) bioassay, in which male and female mice were administered PERC by gavage. In their 1977 report, NCI indicated that PERC, at both the high and low dose levels, induced a statistically significant increase in the incidence of hepatocellular carcinomas in both sexes of B6C3F1 mice. It should be noted that the dose levels used in the NCI study are levels that have been observed, in other experiments, to result in hepatotoxicity. In Osborne-Mendel rats, the resulting high mortality precluded any conclusions with regard to carcinogenic potential. The tetrachloroethylene used in this study was greater than 99 percent pure but was estimated to contain an epichlorohydrin concentration of less than 500 ppm. Based on the dose levels and observed tumor (nasal carcinoma) incidence due to epichlorohydrin in a study conducted by Laskin et al. (1980), it is unlikely that the the response can be attributed to the low levels of epichlorohydrin. The National Toxicology Program (NTP) is testing the possibility that the response was influenced by the impurity in bioassays now in progress, using epichlorohydrin-free PERC.

Some animal studies have not shown PERC to be carcinogenic but they do not negate the conclusions drawn by NCI. Intraperitoneal injection of PERC in strain A mice induced no statistically significant incidence of pulmonary adenomas. In another study in which PERC was applied to mouse skin 3 times per week for the lifetime of the animals, induction of skin tumors was not observed. No conclusions can be made about the carcinogenicity of PERC in Sprague-Dawley rats exposed for 12 months because of the low dose used in this inhalation experiment.

There is only suggestive evidence that exposure of humans to PERC is associated with induction of cancer. There are several epidemiological studies in progress, involving laundry and dry cleaning workers with a history of long exposure to PERC. The preliminary nature of the results preclude any further evaluation at this time.

Tetrachloroethylene has not been clearly demonstrated to cause point mutations in bacteria. There are data that suggest that PERC may be genetically active in yeast. These results, however, do not permit a final judgement on the mutagenic potential of tetrachloroethylene but reinforce the need for further testing.

On the basis of limited available data, it is not possible to define the full potential of PERC to produce adverse teratogenic or reproductive effects. The teratology studies in rats, mice, and rabbits used only single doses of PERC which produced signs of maternal toxicity. Of particular concern is the observation that PERC is preferentially concentrated in maternal milk; thus, nursing infants may represent a special risk group.

1.3.2 Acute, Subchronic, and Chronic Toxicity

Acute exposure to high levels ($\simeq$ 4,000 ppm; 27,120 mg/m^3) of PERC may be fatal, resulting from dysfunction of the central nervous system (CNS). The first gross signs (decrements in task performance and coordination) of CNS depression and behavioral alterations have been observed in controlled human studies in which individuals were exposed to about 100 ppm (678 mg/m^3) for up to 7 hours. It should be noted that more sensitive tests (coordination and EEG patterns) of CNS depression may reveal that PERC affects the nervous system at even lower concentrations.

Both acute and chronic exposure situations have the potential to cause liver damage in humans. While there are insufficient data to estimate the lowest level of PERC that would cause liver damage upon acute or prolonged exposure, the evidence suggests that adverse effects upon the liver can occur at exposure levels that would cause only slight CNS depression. Since PERC has the potential to accumulate in lipid-rich body tissues and is only completely eliminated from the body several weeks after cessation of exposure, prolonged exposure may result in a greater body burden, subjecting the liver to a chronic insult at a given exposure concentration.

In animals, intermittent or prolonged exposure to PERC has been observed to result in liver and kidney damage at levels exceeding 200 ppm (1,356 mg/m^3). This suggests that the lowest-observed-adverse-effect level (LOAEL) (100 ppm; 678 mg/m^3) may not be sufficiently protective of human health with regard to liver and kidney toxicity. In this context, the LOAEL is defined as the lowest exposure level in a study or group of studies which produces statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

1.4 SIGNIFICANCE OF PERC TO HUMAN HEALTH

In real-life situations, the general population is exposed to PERC and its transformation products from a variety of sources: (1) occupational exposures, (2) indoor exposures other than occupational, (3) inhalation of ambient air, and (4) ingestion of contaminated food and drinking water.

When one considers that PERC is a potential human carcinogen, any exposure carries some degree of hazard. With other adverse health effects, exposure levels, duration of exposure, and persistence in the body are important determinants of the manifestation of the adverse effects in question. Certain subgroups of the population may be at a greater hazard than others. These subgroups include (1) pregnant women, (2) children and nursing infants, and (3) those exposed occupationally. While exposure to PERC is an important health concern, other substances that arise during the transformation of PERC in ambient air, or via its metabolism may add to the body burden. Phosgene, a principal atmospheric degradation product, is a known respiratory toxicant. However, at the levels (sub ppb) encountered in ambient air, overt damage would not be expected. Chloroacetyl chlorides, also likely to be produced in ambient air during transformation of PERC, are highly corrosive substances and

may further add to the body burden. Other candidates for scientific inquiry into effects upon health are the metabolites of PERC, trichloroacetic acid and trichloroethanol.

2. INTRODUCTION

Tetrachloroethylene (PERC) is one member of a family of unsaturated chlorinated aliphatic compounds. Other common names/acronyms are perchloroethylene, Perk, PER, and PCE. Its trade names or synonyms include: Carbon dichloride, Perclene, Perclene-D, Tetrachloroethene, Perchlor, Perchlor HDC, Dee-Solv, Dow-Per, Percosolv, Tetravec, and 1,1,2,2-tetrachloroethylene.

Tetrachloroethylene, while a water and solid waste contaminant, is primarily of interest in ambient air exposure situations. It is released into ambient air as a result of evaporative losses during production, storage, and/or use. It is not known to be generated from natural sources. It is photochemically reactive in the troposphere and is removed by scavenging mechanisms.

The scientific data base is limited with reference to the effects of PERC on humans. Effects upon humans have generally been ascertained from studies involving individuals occupationally or accidentally exposed. During such exposures, the concentrations associated with adverse effects on human health were either unknown or far in excess of concentrations found or expected in ambient air. Controlled exposure studies have principally been directed toward elucidating the pharmacokinetic parameters of PERC exposure.

Efforts to determine the effect of multimedia exposures upon human health are complicated by a number of factors. As with any pollutant, PERC comprises only a small portion of a complex array of pollutants in ambient air and in water. Adverse effects may result from exposure to PERC, to a mix of the halocarbon and other pollutants, or to the products of atmospheric interactions of PERC and other compounds.

Since epidemiological studies have not been able to assess adequately the overall impact of PERC on human health, it has been necessary to rely greatly on animal studies to derive indications of potential harmful effects. While animal data cannot always be extrapolated to humans, indications of probable or likely effects among animal species increase confidence that similar effects may occur in humans.

This document is intended to provide an evaluation of the scientific data base concerning PERC. It is believed that the literature has been comprehensively reviewed and critically evaluated, through November 1981. The publications cited in this document represent a majority of the known scientific references to PERC. Reports which had little or no bearing upon the issues discussed were not cited. Some topic areas, such as effects on terrestrial ecosystems, are only briefly discussed or alluded to. Such topics reflect the nature of the scientific data base.

3. TETRACHLOROETHYLENE: BACKGROUND INFORMATION

3.1 PHYSICAL AND CHEMICAL PROPERTIES

Tetrachloroethylene, also called PERC (1,1,2,2-tetrachloroethylene or perchloroethylene) is a colorless, heavy liquid with a chloroform-like odor. It may be used as a solvent for organic substances and is commercially important as a solvent in the dry cleaning of fabrics and in the degreasing of metals. It has a molecular weight of 165.85 and is relatively insoluble in water (150 mg/l) (Handbook of Chemistry and Physics, 1976; Chemical and Process Technology Encyclopedia, 1974).

Its CAS registry number is 127184. In air, at standard temperature and pressure, 1 part-per-million (ppm) is equivalent to 6.8 mg/m^3.

Tetrachloroethylene is photochemically active and, in the troposphere, is decomposed via free radial mechanisms. Under simulated atmospheric conditions in the laboratory, ozone, phosgene, carbon tetrachloride, trichloroacetyl chloride, and formic acid have been identified as transformation products.

When in contact with water for prolonged periods, PERC slowly decomposes to yield trichloroacetic and hydrochloric acids. Upon prolonged storage in light, it slowly decomposes to trichloroacetyl chloride and phosgene by autooxidation (Hardie, 1966). At 700°C, it decomposes when in contact witn activated charcoal, to hexachloroethane and hexachlorobenzene (Gonikberg, 1956). Tetrachloroethylene has a boiling point 121.1°C at 760 mm Hg and a vapor pressure of 14 torr at 20°C. An average experimental evaporative half-life of 27 minutes has been reported (Dilling, 1977).

Tetrachloroethylene is subject to free radical attack by many species, e.g., the chlorine free radical (Cl·) and the hydroxyl free radical (·OH). The hydroxyl free radical reaction represents the principal pathway by which PERC is scavenged from the atmosphere.

The chemical reactivity of PERC has been discussed by Bonse and Henschler (1976) in terms of the electron-inductive effect of the chlorine atoms, which reduce electron density about the ethylene bond. This effect, in combination with a teric protective effect afforded by the chlorine atoms, provides increased stability against electrophilic attack. This is exemplified in the reaction of PERC with ozone. Compared to ethylene and less-substituted chlorination hydrocarbons, PERC has a low rate of reaction (Williamson and Cvetanovik, 1968).

3.2 PRODUCTION

Tetrachloroethylene may be produced by several processes:

1. Chlorination of trichloroethylene:

$$CHCl = CCl_2 + Cl_2 \xrightarrow[SbCl_3]{80°C} CHCl_2\,CCl_3$$

$$2CHCl_2CCl_3 + Ca(OH)_2 \xrightarrow{80°C} Cl_2C = CCl_2 + CaCl_2 + 2H_2O$$

2. Dehydrochlorination of S-tetrachloroethane:

$$CHCl_2\text{-}CHCl_2 + Cl_2 \longrightarrow CCl_2 = CCl_2 + 2HCl$$

3. Oxygenation of S-tetrachloroethane:

$$2CHCl_2CHCl_2 + O_2 \longrightarrow 2CCl_2 = CCl_2 + 2H_2O$$

4. Chlorination of acetylene:

$$CCl_2 = CCl_2 + Cl_2 \xrightarrow{200°C} CCl_3\text{-}CCl_3$$

$$CH \equiv CH + 3\,CCl_3CCl_3 \xrightarrow[\text{catalyst}]{200\text{-}400°C} 4CCl_2 = CCl_2 + 2HCl$$

5. Chlorination of hydrocarbons:

$$\underset{\text{(propane)}}{C_3H_8} + 8\,Cl_2 \longrightarrow CCl_2 = CCl_2 + CCl_4 + 8HCl$$

$$2CCl_4 \longrightarrow CCl_2 = CCl_2 + 2Cl_2$$

6. Oxychlorination of 1,2-dichloroethane:

$$2C_2H_4Cl_2 + 5Cl_2 \longrightarrow C_2H_2Cl_4 + C_2HCl_5 + 5HCl$$

$$C_2H_2Cl_4 + C_2HCl_5 \longrightarrow C_2HCl_3 + 2HCl + CCl_2 = CCl_2$$

$$7HCl + 1.75\ O_2 \longrightarrow 3.5\ H_2O + 3.5\ Cl_2$$

$$2C_2H_4Cl_2 + 1.5\ Cl_2 + 1.75\ O_2 \longrightarrow C_2HCl_3 + CCl_2 = CCl_2 + 3.5\ H_2O$$

The majority of PERC production in the United States is derived from the oxychlorination of 1,2-dichloroethane or via pyrolysis of hydrocarbons (Lowenheim and Moran, 1975).

In 1980, 295,000 metric tons of PERC was produced (Chemical Purchasing, 1980). This represented a 16 percent decrease over reported production for 1979. Production figures were supplied from the International Trade Commission.

For the period 1968-1973, the world production growth rate was 6 percent per year (Shamel et al., 1975). Decreased use as a chemical intermediate and competition from other dry cleaning solvents (petroleum-based), is likely to limit growth in the United States to 1 or 2 percent from 1978 to 1983 (Chemical Marketing Reporter, 1979b).

The major producers and production capacities are shown in Table 3-1. Locations of U.S. production facilities are shown in Figure 3-1.

Imports of PERC may be sizeable although they are partially offset by exports. During April and May 1978, 7,200 metric tons of PERC were imported (Chemical Marketing Reporter, 1978a). During the same period, exports totalled 5,800 metric tons (Chemical Marketing Reporter, 1978 b,c). Most of the PERC imported is produced in Belgium, Italy, France, and Canada (Chemical Marketing Reporter, 1979a).

TABLE 3-1. MAJOR U.S. PRODUCERS OF TETRACHLOROETHYLENE*

Organization	Yearly capacity, tons
Dow Chemical	150,000
PPG	120,000
Vulcan	95,000
Diamond Shamrock	82,500
Ethyl Corporation	50,000
Stauffer Chemical	35,000
E. I. du Pont de Nemours	not reported
Occidental Petroleum	not reported

*Adapted from Chemical Marketing Reporter, 1978c.

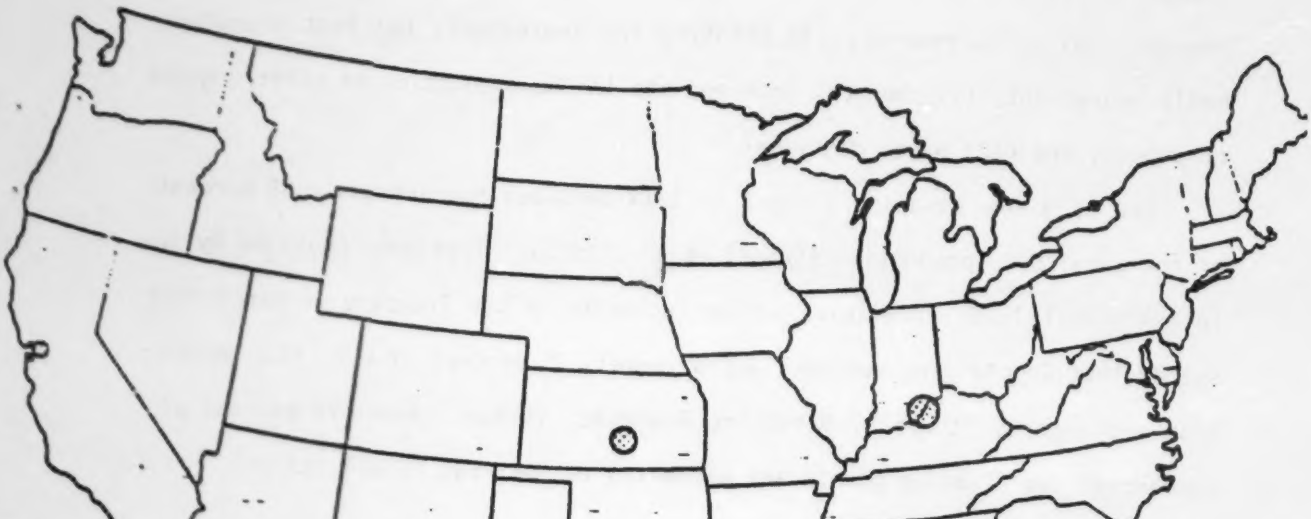
= 100 million pounds

Figure 3-1. Locations of U.S. tetrachloroethylene production facilities producing more than 100 million pounds (Fuller, 1976).

3.3 USE

Tetrachloroethylene has the following uses (Gosselin et al., 1976; Fishbein, 1977):

(1) dry cleaning solvent; (2) textile scouring solvent; (3) dried vegetable fumigant; (4) rug and upholstery cleaner; (5) stain, spot, lipstick, and rust remover; (6) paint remover; (7) printing ink ingredient; (8) heat transfer media ingredient; (9) chemical intermediate in the production of other organic compounds; and (10) metal degreaser.

Use as a dry cleaning solvent in 1973 consumed approximately 65 percent of the total U.S. production (Shamel et al., 1975). Testimony provided by the International Trade Commission to the Secretary of the Treasury in March 1979 stated that drycleaning consumes approximately 75 percent of U.S. PERC production and imports (Chemical Marketing Reporter, 1979a). About 72 percent of commercial dry cleaning plants are estimated to use PERC (USEPA, 1979).

3.4 EMISSIONS

Emissions of tetrachloroethylene arise during its production, use as a chemical intermediate in industrial processes, from storage containers, during disposal, and use as a solvent. Because emissions are almost exclusively to the atmosphere, the information presented in this section focuses upon air. Little data are available concerning discharges to water. The section dealing with monitoring indicates that discharges to water most probably occur. Emissions estimates reflect a diversity of sources throughout the country. Dry cleaning operations are located primarily in urban areas. Approximately 26,000 establishments are estimated to exist according to Bureau of Census data (USEPA, 1979).

Lillian et al. (1975) estimated annual worldwide emissions of PERC (1974) into the troposphere at 450,000 metric tons. Singh (1977a), taking into account historical use and production patterns, estimated that emissions to May 1976 were 11.7 million metric tons. In 1977, global emissions were estimated at 570,000 ± 285,000 metric tons (Singh et al., 1979). Singh et al. (1979) estimated that emissions accounted for approximately 90 percent of the amount of PERC produced (300,000 metric tons) in the United States. Snelson et al. (1978) estimated worldwide emissions in 1973 at 622,700 metric tons (83 percent of 1973 worldwide production). The authors estimated the U.S. contribution to worldwide emissions at 45 percent. Shamel et al. (1975) estimated that emissions of PERC in the United States in 1973 were 272,000 metric tons. Use as a dry cleaning and textile processing solvent were estimated to account for 77 percent of total estimated U.S. emissions (Shamel et al., 1975). The authors estimated the U.S. contribution to worldwide emissions (609,000 metric tons) at 45 percent. Using data obtained from the literature, government agencies, and industrial companies, Eimutis and Quill (1977) estimated that annual emissions of PERC from degreasing operations were 77,885 metric tons.

3.5 ENVIRONMENTAL FATE AND TRANSPORT

The potential for ambient air and water mixing ratios of PERC to pose a hazard to human health is influenced by many processes. Such factors include: (1) transformation into secondary pollutants of concern, and (2) degradation rates in air and water.

3.5.1 Ambient Air

3.5.1.1 Tropospheric Reactivity--Concern that PERC may participate, in a measurable degree, in ozone (O_3) destruction mechanisms in the stratosphere is allayed by recent information that the tropospheric residence time of PERC is 1 year or less (Altshuller, 1980; Singh et al., 1978a; Singh, 1977a). This estimate (16 weeks to 1 year) is longer than previously believed (Crutzen et al., 1978; Lillian et al., 1975; Yung et al., 1975; Pearson and McConnell, 1975). The longer residence time is a result of downward revisions in the estimates of ·OH levels in the troposphere.

Reaction with ·OH is the principal process by which many organic compounds, including PERC, are scavenged from the troposphere. Hydroxyl radicals are produced when O_3 is irradiated, resulting in excited atomic oxygen [O1(D)], which then reacts with water vapor. The tropospheric lifetime of a compound is related to the ·OH mixing ratio according to the expression:

$$\tau_{\text{lifetime}} = \frac{1}{k\,[\text{OH}]}$$

where k is the rate constant of reaction.

Singh and coworkers (Singh et al., 1978a; Singh, 1977a), using an atmospheric budget model, calculated an average ·OH mixing ratio of 2×10^5 to 6×10^5 molecules cm^{-3}. A tropospheric lifetime for PERC of 21 ± 5 weeks was calculated. From the isopleth modelling approach of Crutzen and Fishman (1977) a similar average mixing ratio of ·OH (2×10^5 to 4×10^5 molecules CM^3) was derived.

Altshuller (1980) used an average ·OH mixing ratio of 3×10^5 molecules cm^{-3} and the kinetic data of Chang and Kaufman (1977) in calculating a tropospheric lifetime of 1 year. Chang and Kaufman (1977) had calculated a tropospheric lifetime of 19 weeks, and estimate based, in part, on a surface ·OH mixing ratio of 1×10^6 molecules cm^{-3}. Based on an average daily mixing ratio for ·OH of 1×10^6 molecules cm^{-3} (equivalent to a daytime abundance of 2×10^6 molecules cm^{-3}, Singh et al. (1979a) calculated a lifetime (@ 300°K) for PERC of 68 days. Justification for this ·OH mixing ratio stems from the field measurements of Calvert (1976). At a seasonally averaged ·OH mixing ratio of 4×10^5 molecules cm^{-3} (a level supported by the field measurements of Campbell et al., 1979) and a weighted global average temperature of 265°K, the average lifetime of PERC was calculated to be 292 days or 0.8 years (Singh et al., 1979a).

As the tropospheric lifetime for PERC would be expected to increase as the ·OH mixing ratio decreased, ·OH reaction mechanisms have a direct bearing on the amount of PERC that can diffuse into the stratosphere. If current estimates of a lower ·OH abundance are correct, approximately 2 or 3 percent of the tropospheric PERC could diffuse into the stratosphere (Singh, 1978).

Higher levels of ·OH have been reported for the southern hemisphere compared to those in the northern hemisphere (Singh, 1978). This gradient probably is due to the fact that carbon monoxide levels are much higher in the northern hemisphere, thus reducing ·OH levels (Singh, 1978). Measurements of PERC and other reactive halocarbons indicate that mixing ratios are higher in the northern hemisphere (where the ·OH mixing ratio is low) and where most of the PERC is released (Singh et al., 1978b).

Chamber studies indicate that PERC, upon irradiation and reaction in the troposphere, can be transformed into a number of secondary products. Lillian et al. (1975) irradiated a mixture of PERC, nitrogen dioxide, and reactive hydrocarbon (60 percent paraffin, 13 percent olefin, and 27 percent aromatic). The levels were: PERC, 700 ppb (4.7 mg/m^3); nitrogen dioxide, 500 ppb (0.94 mg/m^3); hydrocarbon, 1,000 ppb. During 13 hours or irradiation, the mixing ratio of PERC decreased. During this decrease, an increase in the amount of phosgene was observed. The conversion, on the basis of chlorine, to phosgene was 60 percent. For this determination, 800 ppb (5.4 mg/m^3) PERC and 500 ppb (0.94 mg/m^3) nitrogen dioxide was irradiated in an atmosphere in which the relative humidity was 50 percent. The maximum phosgene mixing ratio ratio observed was 0.95 ppm. It was estimated, on the basis of the observed results, that an ambient PERC mixing ratio of 10 ppb (0.068 mg/m^3), such as that observed in New York City, could lead to the formation of 12 ppb phosgene.

Phosgene also was observed as a degradation product of PERC in the experiments of Huybrechts et al. (1967). They observed a yield of 85 ± 5 percent trichloroacetyl chloride and 15 ± 5 percent phosgene, when PERC was irradiated in the presence of oxygen. Trace quantities of carbon tetrachloride (CCl_4) and tetrachloroethylene epoxide were also reported.

Mathias et al. (1974) observed phosgene to be the major product when PERC was irradiated in an oxygen-enriched environment. Tetrachloroethylene epoxide, observed when PERC was irradiated in the presence of only ozone, was not formed in the presence of oxygen.

Phosgene and a variety of other products were reported in the chamber study of Gay et al. (1976). A mixture of PERC (5,000 ppb; 33.9 mb/m^3) and nitrogen dioxide (1,800 ppb; 3.4 mg/m^3) was irradiated with ultraviolet radiation. Products observed included ozone, hydrogen chloride, carbon monoxide, formic acid, phosgene, and trichloroacetyl chloride. Seven percent of the PERC reacted after 140 minutes of irradiation. The amount of hydrogen chloride formed was almost four times the amount of phosgene produced. Compared to vinyl chloride, trichloroethylene, 1,2-dichloroethylene, ethylene, and 1,1-dichloroethylene, the reactivity of PERC was low. The slow rate of disappearance of PERC under these conditions is indicative that free chlorine radicals did not participate to any significant degree. Carbon tetrachloride was not reported to be a transformation product.

Singh et al. (1975) reported that trichloroacetyl chloride may undergo heterogenous reactions to form CCl_4. It was observed experimentally that CCl_4 was formed when PERC, in air, was irradiated. Mixing ratios of CCl_4 continued to increase after all the PERC had reacted. At the same time, trichloroacetyl chloride continued to react, suggesting a role as a CCl_4 precursor. Photodecomposition of PERC over 7 days led to the formation (w/w) of about 8 percent

CCl_4 and 70 to 85 percent phosgene. Singh and coworkers concluded that under these simulated tropospheric conditions, that after photolysis of PERC, chlorine-sensitized photooxidation occurs (Singh et al., 1975).

It is cautioned that these simulated reaction conditions and observations may not be representative of what takes place in real atmospheres. Singh (1978) suggested that trichloroacetyl chloride may undergo surface reactions in the gas chromatograph to form CCl_4.

In the absence of irradiation, PERC has been reported as either unreactive or slowly reactive with ozone, nitric oxide, and nitrogen dioxide (Lillian et al., 1975). A slow rate of reaction between PERC and ozone also has been observed by Williamson and Cvetanovic (1968).

Using rate data (Atkinson et al., 1978) pertaining to the reaction of PERC with ozone and ·OH, Altshuller (1980) calculated that PERC reacts 3×10^3 more rapidly with ·OH than with ozone. Assuming an average ·OH mixing ratio of 3×10^5 molecules cm^{-3}, the rate of reaction was 5×10^{-8}. In reaction with ozone, an average ozone mixing ratio of 10^{12} molecules cm^{-3} was used, leading to a calculated rate of 1.5×10^{-11}.

3.5.1.2 Tropospheric Removal Mechanisms for PERC--The reaction sequence by which PERC may be scavenged from the troposphere is as follows (Graedel, 1978):

$$C_2Cl_4 + HO\cdot \longrightarrow HOC(Cl)_2C(Cl)_2\cdot$$

$$HOC(Cl)_2C(Cl)_2\cdot + O_2 \longrightarrow HOC(Cl)_2C(Cl)_2O_2\cdot$$

$$HOC(Cl)_2C(Cl)_2O_2\cdot \xrightarrow[\text{abstraction}]{\text{oxygen}} HOC(Cl)_2C(Cl)_2O\cdot$$

$$HOC(Cl)_2C(Cl)_2O\cdot \longrightarrow HOC(Cl)_2\cdot + COCl_2$$

$$HOC(Cl)_2\cdot + O_2 \longrightarrow COCl_2 + HO_2\cdot$$

Howard (1976) suggested that the reaction path for the atmospheric oxidation of PERC may follow the scheme below, leading to the production of oxalochloride:

$$C_2Cl_4 + \cdot OH \longrightarrow C_2Cl_2OH\cdot$$

$$\longrightarrow CCl_2CClOH\cdot + Cl\cdot$$

$$CCl_2CCl_2OH\cdot + O_2 \longrightarrow O_2CCl_2CCl_2OH$$

$$O_2CCl_2CCl_2OH + NO \longrightarrow COClCCl_2OH\cdot + NO_2 + Cl\cdot$$

$$\cdot OH + COClCCl_2OH \longrightarrow COClCOCl + H_2O + Cl\cdot$$

Compared to other ethylene compounds studies, Howard (1976) reported that PERC exhibits unusually low reactivity toward hydroxyl radicals.

Snelson et al. (1978) suggested that trichloroacetyl chloride and phosgene would hydrolyze to the corresponding chloroacetic acids and hydrogen chloride via homogeneous gas phase hydrolysis. The acids then would presumably be washed out of the atmosphere.

The environmental significance of the production of phosgene from PERC has been discussed by Singh and coworkers (Singh, et al., 1975; Singh, 1976). As PERC emissions are likely to be higher in urban areas, the reactivity of this halocarbon may result in concentrations of phosgene in the low ppb range during adverse meteorological conditions in and around urban centers (Singh, 1976). It should be noted that overt adverse health damage would not be expected at these phosgene levels. There is, however, little information regarding long-term exposure to low ppb levels of phosgene. The results of Singh and coworkers indicate that negligible tropospheric loss via gas phase hydrolysis would be expected since phosgene is very stable in the gas phase. The two important sinks cited were heterogeneous decomposition and slow liquid phase hydrolysis. Singh (1976) concluded that phosgene is removed slowly from the atmosphere. Rainfall appears to lower atmospheric levels of phosgene (Singh et al., 1977b).

The observed diurnal variations in PERC levels suggest that PERC has higher mixing ratios in the morning and evening hours than at other times (Lillian et al., 1975; Singh et al., 1977b). Ohta et al. (1977) reported that mixing ratios tended to be highest on cloudy days and lowest on rainy days.

Solar flux is a major factor in the rate at which PERC is removed from the atmosphere. Singh et al. (1977b) suggested that the reduced solar flux in winter months would permit a much longer transport of PERC because of reduced reactivity. The effect of solar flux was calculated by Altshuller (1980) who estimated that a 1 percent consumption of PERC by reaction with ·OH would take 14 days during the month of January as opposed to one day in July.

The formation of CCl_4 from PERC in the troposphere was reported to be negligible by Howard, (1976), whereas phosgene appears to be a major transformation product. Also, while the studies of Gay et al. (1976) indicate that trichloroacetyl chloride may be formed through chlorine atom migration in an epoxide intermediate, evaluation of ·OH and oxygen atom rate constants indicate that less than 1 percent of PERC in ambient air react with atomic oxygen and, of the activated epoxides formed, only a small percentage undergo rearrangement (Graedel, 1978).

3.5.2 Water

Jensen and Rosenberg (1975) investigated the degradability of PERC in both open and closed systems, with sea water and fresh water. In open aquaria, with 20ℓ of sea water, PERC levels decreased 50 percent within 200 hours (daylight). In a closed system, levels decreased approximately 25 percent over the same interval (daylight). It was reported that PERC levels in boiled, deionized water in a closed system did not exhibit any significant decrease after 8 days. Analysis was by headspace analysis, followed by gas chromatography-electron capture detection (GC-ECD) quantification.

Dilling et al. (1975) reported that PERC, in water, slowly decomposes to form trichloroacetic and hydrochloric acids.

The evaporation rate was determined by dissolving 1 ppm (w/w) PERC in 200 mℓ of water. Solution temperature was approximately 25°C. The solution was stirred magnetically in a sealed system. Quantification was made by mass spectroscopy. The evaporation rate of PERC determined from measurements over a 2-week period, was characterized by a 50 percent decrease in the initial mixing ratio in 24 to 28 minutes. The stirring speed had a marked effect on the evaporation rate. With no stirring, except for 15 seconds every 5 minutes, the time required for 50 percent depletion ranged from 72 to 90 minutes. The evaporative half-life was 27 ± 3 minutes. Addition of dry, granular bentonite clay (500 ppm) appeared to increase the rate of disappearance by 33 percent at 20 minutes. However, when the clay was allowed to remain in contact with purified water for several days and then added to the solution, there was no change in the rate compared with control. In closed system investigations, Dillings et al., used dry, powdered dolomitic limestone, bentonite and peat moss to determine the absorption rate for PERC. With 500 ppm bentonite, there was a 22 percent absorption after 30 minutes. There was no further absorption. Addition of limestone resulted in a 50 percent depletion in 20 ± 2 minutes. Addition of silica sand had no effect on the disappearance rate. When 500 ppm peat moss was added, up to 0.4 ppm PERC was absorbed after 10 minutes. At longer times, no further absorption was observed. It was concluded that evaporation probably is the major pathway by which PERC is lost from water.

In reactivity studies, Dilling et al. (1975) found the sunlight had the greatest effect on the rate of PERC disappearance. The PERC level in water was 6 μM. Over a 12 month period in which PERC solutions were stored in the dark as well as in the light, PERC levels decreased from 1 ppm (0 time), to 0.63 ppm (6 months), to 0.35 ppm (12 months) in samples stored in the dark. In the light-exposed solution, the level decreased to 0.52 ppm (6 months), and 0.24 ppm (12 months).

Schwarzenbach et al. (1979), in measurements of PERC levels in Lake Zurich, reported findings compatible with those of Dilling et al. (1975) in that evaporation is the dominant elimination process from surface waters. The annual release to the atmosphere was estimated by applying a steady-state mass balance model. Based on vertical concentration profiles from the lake, about 240 kg PERC was released from the central basin annually.

3.6 LEVELS OF EXPOSURE

3.6.1. Mixing Ratios

3.6.1.1 Ambient Air--A wide variety of halogenated aliphatic hydrocarbons, including tetrachloroethylene (PERC), have been determined in ambient air. Ambient measurements of PERC have been conducted in both the United States and other areas of the world. These determinations provide a basis for assessing the levels to which human populations may be exposed.

Measured ambient air concentrations differ widely and undoubtedly reflect the influences of a variety of factors, e.g., meteorological conditions, tropospheric reactivity, diurnal variations, and source emissions.

Tables 3-2 and 3-3 provide summary information regarding background and urban concentrations of PERC, respectively.

TABLE 3-2. NONURBAN MEASUREMENTS OF TETRACHLOROETHYLENE

Location	Type of site	Date of measurement/ analytical method	Concentration ppb	Concentration mg/m^3	Reference
White Face Mountains, N. Y.	Nonurban	Sept. 17, 1974 GC/EC	<0.02 to 0.19	$<1.35 \times 10^{-4}$ to 12.8×10^{-4}	Lillian et al., 1975
Sandy Hook, N. J.	Ocean (3 miles offshore)	July 2, 1974 GC/EC	0.15 to 1.4	10.17×10^{-4} to 94.9×10^{-4}	Ibid
San Bernadino Mountains, Calif.	1,800 meters	Fall, 1972 GC/EC	0.09	6.10×10^{-4}	Simmonds et al., 1974
California Coast	Coastal (inward flowing maritime air)		0.01	0.67×10^{-4}	Ibid
Badger Pass, Calif. (Yosemite National Park)	Mountain 2,360 meters elevation	May 12-16, 1976	0.0307 ± 0.0105	$2.08 \times 10^{-4} \pm 0.71 \times 10^{-4}$	Singh et al., 1977b
Point Arena, Calif.	Marine	1976	0.0334 ± 0.0046	2.26×10^{-4} 0.31×10^{-4}	Singh et al., 1978a
Stanford Hills, Calif.	Clean Air	Nov. 24-30, 1975	0.0383 ± 0.0111	$2.59 \times 10^{-4} \pm 0.75 \times 10^{-4}$	Singh et al., 1977c
Point Reyes, Calif.	Clean Air	Dec. 2-12, 1975	0.0431 ± 0.0178	$2.92 \times 10^{-4} \pm 1.2 \times 10^{-4}$	Ibid
North Atlantic Ocean	Ocean	Oct., 1973	0.021 ± 0.003	$1.44 \times 10^{-4} \pm 0.22 \times 10^{-4}$	Lovelock, 1974
Northeast Atlantic Ocean	Ocean		0.0007	4.7×10^{-6}	Murray and Riley, 1973

TABLE 3-3. URBAN CONCENTRATIONS OF TETRACHLOROETHYLENE

Location	Date of Measurement	Concentration, ppb (mg/m^3) Max.	Min.	Average	Reference
Arizona					
Phoenix	Apr. 23-May 6, 1979**	3.696 (0.025)	0.129 (0.0008)	0.9938 ± 0.7155 (0.0067 ± 0.0048)	Singh et al., 1981
California					
Los Angeles	Apr. 29-May 4, 1976	2.267 (0.015)	0.0608 (0.0004)	0.674 ± 0.498 (0.0045 ± 0.0033)	Singh et al., 1978a
Los Angeles	Apr. 9-21, 1979**	2.065 (0.014)	0.173 (0.0011)	1.479 ± 0.444 (0.0100 ± 0.0030)	Singh et al., 1981
Los Angeles Basin	Fall, 1972	3.84 (0.0260)	0.37 (0.0025)	1.25 (0.00847)	Simmonds et al., 1974
Palm Springs	May 5-11, 1976	1.153 (0.0075)	0.0177 (0.00012)	0.278 ± 0.232 (0.00188 ± 0.00157)	Singh et al., 1978a
Pasadena	Fall, 1972	4.2 (0.028)	0.19 (0.0012)	2.2 (0.015)	Simmonds et al., 1974
Riverside	April 25-May 3, 1977	2.325 (0.01577)	0.096 (0.00065)	0.983 ± 0.454 (0.00667 ± 0.00307)	Singh et al., 1978a
Oakland	June 28-July 10, 1979**	1.449 (0.0098)	0.534 (0.003)	0.308 ± 0.291 (0.002 ± 0.001)	Singh et al., 1981
Delaware					
Delaware City	July 8-10, 1974	0.51 (0.0034)	<0.02 (<0.0001)	0.24 (0.0016)	Lillian et al., 1975
Louisiana					
Baton Rouge, Geismar, and Plaquemine	Fall, 1978	0.18 (0.001)	.001 (0.007 × 10^{-3})	0.017 (0.118 × 10^{-3})	Pellizzari et al., 1979b
Maryland					
Baltimore	July 11-12, 1974	0.29 (0.0019)	<0.02 (<0.0001)	0.18 (0.0012)	Lillian et al., 1975
Michigan					
Detroit	Oct 27-Nov 5, 1978**	2.16 (0.004)	<0.1 (<0.001)	0.35 (0.002)	Evans et al., 1979
New Jersey					
Bayonne	March, 1973-Dec., 1973	8.2 (0.0055)	0.30 (0.0020)	1.63 (0.0110)	Lillian et al., 1975
New Brunswick	-	-	0.5 (0.003)	-	Lillian et al., 1976
New Brunswick	-	-	0.12 (0.0081)	-	Lillian et al., 1974
Seagirt	June 18-19, 1974	0.88 (0.059)	0.10 (0.067)	0.32 (0.0022)	Lillian et al., 1975
Fords	Sept. 26-27, 1978**	25 (0.170)	1 (0.007)	-	Pellizzari et al., 1979b
Carlstadt	Sept. 28-29, 1978**	3 (0.025)	0.1 (0.0007)	-	Ibid

TABLE 3-3 (continued)

Location	Date of Measurement	Concentration, ppb (mg/m^3) Max.	Min.	Average	References
Boundbrook, Rahway, Edison and Passaic	Sept 18-22, 1978	58 (0.394)$^{+}$	trace	30.9 (0.210)	Pellizari et al., 1979b
Seagirt	June 18-19, 1974	0.88 (0.059)	0.10 (0.067)	0.32 (0.0022)	Lillian et al., 1975
New York					
New York City	June 27-28, 1974	9.75 (0.0661)	1.0 (0.006)	4.5 (0.030)	Lillian et al., 1975
	Aug 18-27, 1978**	10.61 (0.0721)	0.16 (0.001)	1.00 (0.006)	Evans et al., 1979
Niagara Falls and Buffalo	Fall 1978	2.0 (0.014)	0.02 (0.122 x 10^{-3})	1.0 (0.0068)	Pellizzari et al., 1979b
Texas					
Houston	Sept 16-25, 1978**	4.52 (0.030)	<0.1 (<0.001)	0.11 (0.001)	Evans et al., 1979
Houston, Deer Park, Pasadena, Freeport, and La Porte	Fall 1978	0.29 (0.002)$^{++}$	trace	0.027 (0.189 x 10^{-3})	Pellizzari et al., 1979b; Pellizzari, 1978
England					
Liverpool	March 25, 1972	-	0.01 (0.08 x 10^{-3})	-	Murray and Riley, 1973
Japan					
Tokyo	-	-	1.2 (8.1 x 10^{-3})	-	Ohta et al., 1976

**24-hour value
$^{+}$sampling time: 14 minutes
$^{++}$sampling time: 100 minutes

Evidence for variability in ambient air concentrations is shown by the results of Lillian et al. (1975) at eight U.S. locations. The lowest concentration was reported at Whiteface Mountain, New York (0.03 ppb; 2×10^{-4} mg/m^3). The maximum level recorded was in New York City (10 ppb; 0.067 mg/m^3). Typical levels are shown in Table 3-4. As shown in Figure 3-2, the range of concentrations at each site also was quite variable and was observed to vary by almost an order of magnitude. Figure 3-3 shows the diurnal variation at New York City. The Whiteface Mountain measurement average was at the limit of sensitivity of the gas chromatographic system utilized. The gas chromatograph (GC) was equipped with an electron capture detector and flame ionization detector. Permeation tubes were used for GC calibration. The overall error associated with the analysis was less than ± 15 percent. Tetrachloroethylene could be measured at least 50 percent of the time at all locations at concentrations exceeding 0.06 ppb (4×10^{-4} mg/m^3), and the distribution of the halocarbon was attributed to its tropospheric reactivity. The authors suggested that since sources of PERC are located primarily in urban areas, urban transport plays an important role in its distribution.

A study concerning the ambient air levels of several halogenated hydrocarbons was conducted by Simmonds and co-workers (1974) in the Los Angeles Basin during the fall of 1972. Ambient concentrations were determined over a three-day sampling period at 42 sites. Analyses were made with a gas chromatograph equipped with an electron capture detector used coulometrically. Ambient concentrations were confirmed by comparison with a known solution prepared by multiple dilution. Precision and accuracy of the experimental procedure were not reported. Efforts were reported to have been made to avoid sampling in those areas in close proximity to known users of halocarbons.

TABLE 3-4. TYPICAL LEVELS OF TETRACHLOROETHYLENE* AT SIX U.S. SITES (Lillian et al., 1975)

Date	Time	Location	Type of Site	ppb
6/27/74	11 p.m.	New York City	Urban	1.2
9/17/74	Noon	Whiteface Mountain, NY	Nonurban	0.09
7/2/74	2 p.m.	Sandy Hook, NJ	3 miles offshore	0.73
7/19/74	1 p.m.	Seagirt, NJ	National Guard Base	0.25
7/17/74	12:28 p.m.	Wilmington, OH	5,000 feet elevation above inversion	<0.02
7/17/74	12:03 p.m.	Wilmington, OH	1,500 feet elevation in an inversion layer	0.73

*Quantification was made by GC/EC.

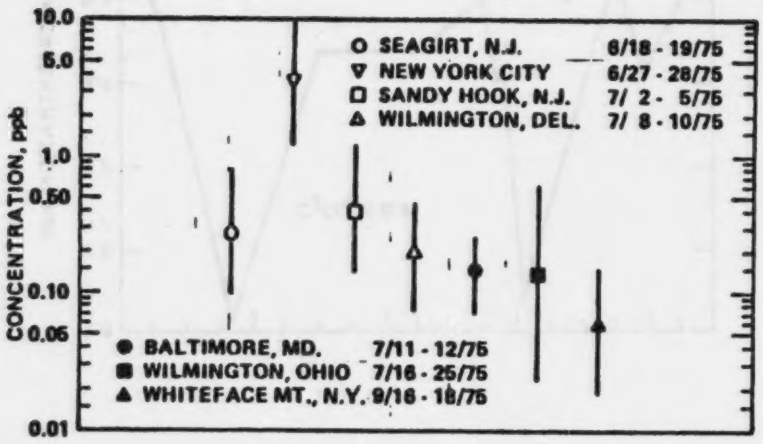

Figure 3-2. Tetrachloroethylene values at various locations. (Lillian et al., 1975)

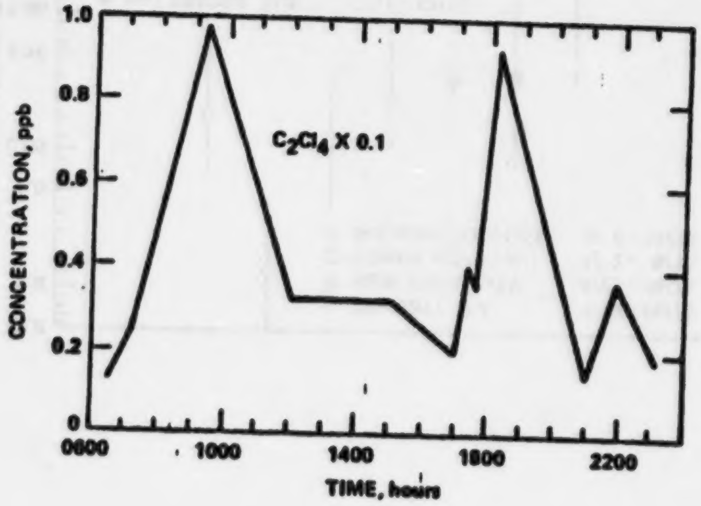

Figure 3-3. Diurnal variations in tetrachloroethylene concentrations in New York City. (Lillian et al., 1975).

The highest concentration of PERC was found in the Pasadena area (4.2 ppb; 0.028 mg/m^3) on a day of visible smog and stable inversion conditions. The lowest concentration was recorded in maritime air flowing inland (less than 0.01 ppb; 0.67 x 10^{-4} mg/m^3). Wind speed was recorded at 10 knots. High concentrations of PERC, judged by the authors to be due to local emissions, were found in the central Los Angeles business district.

Background levels taken at an altitude of 1,800 meters gave a 24-hour average concentration of 0.09 ppb (6.1 x 10^{-4} mg/m^3). Measurements were made in the San Bernadino Mountains during a 48-hour period.

At one coastal site, higher than expected concentrations of PERC were found (2.1 ppb; 0.014 mg/m^3). The investigators conjectured that either meteorological conditions caused an air mass to accumulate in the area or that the average was a result of local emissions.

Vertical profile measurements indicated that the concentration of PERC decreased with altitude. This decrease also was observed above a significant inversion layer at 1,700 meters. Diurnal measurements suggested that PERC was subject to fluctuations over a 24-hour period. Diurnal measurements were conducted in the West San Gabriel Valley. Overall, a progressive decrease in the concentration of PERC, as well as three other halogenated compounds, was seen upon moving from the inland valleys to the coast.

A series of studies on the distribution and levels of halogenated hydrocarbons in ambient air has been conducted by Pellizzari (1978). PERC was detected in the ambient air at measurement sites in New Jersey, California, Louisiana and Texas.

High concentrations were found in the air near a chemical waste disposal site and chemical manufacturing facility in Edison, New Jersey. Four locations, constituting upwind, downwind and crosswind directions, were selected for monitoring. Meteorological conditions at the time of measurement were recorded. Samples of ambient air (twice daily) were taken over a period of three days. Each sampling period was about 2 hours in duration and a volume of 100 to 150 liters was collected. A bed of Tenax GC in a glass cartridge was used to concentrate PERC and other ambient air pollutants. Quantification was made by gas chromatography-mass spectrometry (GC/MS). Tetrachloroethylene was one of six halogenated compounds detected in the ambient air in practically all the samples taken near the disposal site. Downwind sites evidenced higher PERC concentrations than upwind sites. Values reported ranged from trace amounts to a maximum concentration of 58 ppb (0.394 mg/m^3). The maximum concentration was recorded in the ambient air at the waste disposal site.

In Texas, PERC was detected in the ambient air at 15 of 18 locations. The site locations were selected on the basis of their proximity to areas of chemical manufacture and storage and transport facilities. The highest recorded concentrations were 0.29 ppb (1.9×10^{-3} mg/m^3) and 0.23 ppb (1.5×10^{-3} mg/m^3) at two sites. Concentrations measured at other sites were less than 0.012 ppb (0.81×10^{-4} mg/m^3). Site locations included several in the Houston area, Pasadena, Deer Park, Freeport, and La Porte. Levels of PERC are presented in Table 3-3.

Tetrachloroethylene also was detected in the ambient air at 4 of 5 sites in Geismar, Louisiana, an area of chemical industry and production of PERC. While detected at the upwind and crosswind measuring sites, it was not detected at the downwind site. The estimated highest concentration of PERC was 0.014 ppb (0.95×10^{-4} mg/m^3).

More recently, Pellizzari and coworkers (1979b) have extended their measurements of PERC in ambient air to include monitoring in the "Old" Love

Canal area in New York State. Levels were measured during 1978 near Niagara Falls and Buffalo, New York; Rahway/Woodbridge, Boundbrook, Edison, Passaic, and Fords, New Jersey; Baton Rouge, Geismar, New Orleans, and Plaquemine, Louisiana; and near Houston, Deer Park, and Pasadena, Texas. Levels are included in Table 3-3. The investigators termed PERC a "ubiquitous" air contaminant in each of these areas.

Analysis (1975) of ground level air for PERC at a location (Midland County, Michigan) 200 miles downwind from Chicago gave PERC concentrations of 30 to 50 ppt (0.2×10^{-3} to 0.3×10^{-3} mg/m^3). Analysis was performed by pre-concentrating air samples prior to temperature-programmed GC-ECD determinations. Identity and quantification were confirmed by GC-MS (Russell and Shadoff, 1977)

Measurements of PERC concentrations in urban, rural, and marine environments have been made by Singh et al. (Singh et al., 1978a; Singh et al., 1977b) Singh et al., 1978b; Singh, 1976; Singh et al., 1977c; Singh et al., 1981) using a GC/EC method. Ambient air samples from Menlo Park, California (urban) averaged 0.11 ppb (0.74×10^{-3} mg/m^3) PERC (Singh et al., 1978a). Measurements in Badger Pass, California (clean air), at an elevation of 2,360 meters, gave an average concentration of 0.0307 ± 0.0105 ppb ($2.08 \times 10^{-4} \pm 0.71 \times 10^{-4}$ mg/m^3) (Singh et al., 1977c). The coefficient of variation was 34 percent. Singh et al. (1977b) used the Badger Pass measurements as representative of the northern hemisphere background concentrations in the lower troposphere. Point Arena, a clean air site in the marine environment, gave an average concentration of 0.0334 ± 0.0046 ppb ($2.26 \times 10^{-4} \pm 0.31 \times 10^{-4}$ mg/m^3) when measured in May 1977 (Singh et al. 1978a). These data were reported by Singh and coworkers to be representative of the average background concentration in the marine environment of the northern hemisphere. The coefficient of variation was 14 percent. Both sites were representative for background levels. At Reese River, Nevada (elevation 1,982 meters), an average PERC mixing ratio of 0.0318 ± 0.0031 ppb ($2.1 \times 10^{-4} \pm 0.21 \times 10^{-4}$ mg/m^3) was reported (Singh et al., 1978a). The coefficient of variation was 10 percent. Quantification was made by GC/ECD operated coulometrically.

Mill Valley, California, a site that may be affected by urban transport, had an average PERC mixing ratio of 0.0652 ± 0.0489 ppb ($2.57 \times 10^{-3} \pm 0.33 \times 10^{-3}$ mg/m^3). The coefficient of variation was 75 percent. Riverside, California, an urban location, had an average mixing ratio of 0.9832 ± 0.4541 ppb ($6.6 \times 10^{-3} \pm 3.0 \times 10^{-3}$ mg/m^3). The coefficient of variation was 46 percent.

Subsequent measurements of ground-level samples by Singh et al. (1978b) in both the northern and southern hemispheres gave average background levels of 0.040 ± 0.012 ppb ($2.7 \times 10^{-4} \pm 0.08 \times 10^{-4}$ mg/m^3) and 0.012 ± 0.003 ppb ($0.081 \times 10^{-3} \pm 0.02 \times 10^{-3}$ mg/m^3), respectively. Globally, the average background level of PERC was 0.026 ± 0.007 ppb ($1.7 \times 10^{-4} \pm 0.47 \times 10^{-4}$ mg/m^3); the coefficient of variation was 27 percent.

Tetrachloroethylene was judged by Singh and co-workers to be ubiquitous as it was measured 100 percent of the time (Singh et al., 1978a). In the studies by Singh, the average urban level of PERC was 30 times the background mixing ratio.

Phosgene, an expected photooxidation product of PERC was found to have a 24-hour average background level of 0.22 ppb (0.149 μg/m^3) at Badger Pass, California (Singh et al., 1976). Urban levels of phosgene in Los Angeles and Menlo Park averaged about 0.030 ppb (0.203 μg/m^3). The range of phosgene levels at all sites was 0.013 to 0.061 ppb (0.088 to 0.414 μg/m^3).

The two major products of the photochemical oxidation of chloroethylenes are likely to be phosgene and chloroacetyl chlorides (Singh et al., 1978a). Methods for accurately measuring low levels of chloroacetyl chlorides are not currently available.

Singh et al. (1977b) in two ground-level field studies conducted in California (Stanford Hills and Point Reyes), found an average background level of 0.0407 ± 0.0144 ppb ($2.76 \times 10^{-4} \pm 0.97 \times 10^{-4}$ mg/m^3) PERC. The coefficient of variation was 35 percent. Tetrachloroethylene was identified using retention time and ionization efficiency. Calibrations were performed using standard multiple dilution procedures starting with pure material. The sample size was 5.8 ml. Monitoring was established at each site on a 24 hour per day basis. The lower detection limit was reported as 0.005 ppb (0.3×10^{-4} mg/m^3). The overall accuracy of measurements was reported as ± 10 percent. The authors indicated that the slightly higher concentration measured at one of the sites was caused by a nearby emissions source. When winds were blowing from the source, a maximum concentration of 3.7 ppb (0.025 mg/m^3) was recorded. The maximum concentration recorded at the other site was 2.49 ppb (0.016 mg/m^3).

In recent field studies at Los Angeles, Phoenix, and Oakland (California), Singh et al. detected PERC levels as high as 3.7 ppb (0.022 mg/m^3), in Phoenix. Levels are shown in Table 3-3. Samples were preconcentrated cryogenically. Analyses were performed using GC/ECD in a mobile laboratory. Primary standards were generated with permeation tubes of TFE Teflon.® Permeation rate errors were < ± 5 percent.

Tetrachloroethylene was monitored at ten sites within each of three metropolitan areas (New York City, Houston, and metropolitan Detroit) by the U.S. Environmental Protection Agency (Evans et al., 1979; Evans, 1981). Mixing ratios are shown in Table 3-3. Sampling was conducted from 18 August 1978 through 5 November 1979. Observed levels ranged from 0.2 to 10.6 ppb in

New York City; from below detectable (<.1) to 4.5 ppb in Houston, and from below detectable to 2.2 ppb in Detroit. Significant day-of-week variations were apparent. Method of analysis was based on collection of 24-hour samples on activated charcoal, desorption by carbon disulfide (CS_2)/methanol, separation by gas chromatography and detection by ECD.

Nearly half of the Houston samples and 12 percent of the Detroit samples fell below the detection limit (0.1 ppb; 0.68 mg/m^3) while all samples collected in New York City exceeded the detection limit and half exceeded 1 ppb. Background concentrations occurring at nonurban and downwind locations appear to be below the detection limit. The estimated coefficient of variation for the analytical technique is 6.6 percent, with 95 percent confidence that the true value falls between 4.9 and 8.3 percent. The coefficient of the measurement method was estimated at 16.2 percent, with 95 percent confidence that the true value falls between 13.2 and 19.2 percent. This latter estimate includes variability due to sample collection, handling, and desorption. It was concluded that ambient levels in urban areas are proportional to population density (Evans, 1980).

Howie (1980) reported ambient air levels of PERC in the vicinity of laundries to be as high as 32 ppb (0.22 mg/m^3). In this study of indoor PERC concentrations, outdoor samples provided background data. Measurements were made by adsorbing PERC onto charcoal filters, followed by desorption with carbon disulfide and quantification by GC-ECD and GC-MS. Outdoor samples were collected for 24 hours. Of 124 measured samples, 56 had 24-hour levels of less than 1 ppb.

In comparison, the range of indoor concentrations, as measured by flame ionization detection, was from about 100 ppb (0.678 mg/m^3) to about 10,000 ppb (67.8 mg/m^3). Replicate sample analyses were reported to give an overall precision of better than 20 percent for both indoor and outdoor samples.

An average tropospheric background concentration of 0.0156 ± 0.0046 ppb ($0.105 \times 10^{-3} \pm 0.031 \times 10^{-3}$ mg/m^3 PERC was obtained over the Pacific northwest (48°N), in March 1976, by Cronn et al. (1977). The coefficient of variation was 30 percent. Quantification was made by GC/ECD of 37 samples (500 ml each) of air after component separation by a freeze-out method. Instrument calibrations were performed by static dilution of standards. Tetrachloroethylene was barely detectable 15,000 to 20,000 feet above the tropopause. In April 1977, collection and analysis of 26 air samples obtained at 37°N resulted in an average tropospheric background concentration of 0.0099 ± 0.0047 ppb ($0.67 \times 10^{-4} \pm 0.32 \times 10^{-4}$ mg/m^3) PERC (Lovelock 1974). The coefficient of variation was 48 percent.

The detection of ambient air levels of PERC also has been reported from Western Ireland, Japan, Great Britain, Germany, France, Belgium, Italy, and the Atlantic Ocean. Measurements made by Lovelock (1974) over Western Ireland during June and July of 1974 indicated an average concentration of 0.028 ± 0.009 ppb ($1.89 \times 10^{-4} \pm 0.61 \times 10^{-4}$ mg/m^3). The coefficient of variation was 32 percent. Similar concentrations were obtained by Lovelock in the tropospheric air over the north Atlantic Ocean during October 1973. The concentration was 0.021 ± 0.003 ppb ($1.44 \times 10^{-4} \pm 0.22 \times 10^{-4}$ mg/m^3). The analytical procedure used was GC/ECD. Tetrachloroethylene was characterized by retention time only.

Measurements taken in the ambient air over tne northeast Atlantic Ocean by Murray and Riley (1973) yielded an average mixing ratio of 0.7×10^{-3} ppb (4.7×10^{-6} mg/m^3). The concentration reported was 5 mg/m^3. The range of measurements during this study varied between 0.1×10^{-3} to 0.9×10^{-3} ppb (0.67×10^{-6} to 6.1×10^{-6} mg/m^3). Measurements were made at 11 sites. In contrast, higher levels were found in the ambient air over rural and developed areas of Britain. The average level of PERC in the air over four sites was found to be 0.0028 ppb (19 x 10^{-6} mg/m^{3}). A gas chromatograph equipped with an electron capture detector was used. The estimated coefficient of variation of the method was reported as less than 15 percent.

Ground-level measurements made by Cox et al. (1976) in the northern hemisphere (Cork, Ireland) in 1974 resulted in an average PERC mixing ratio of 0.0276 ± 0.0093 ppb (0.187 x 10^{-3} ± 0.063 x 10^{-3} mg/m^{3}). Analyses were performed by GC/EC. The coefficient of variation was 34 percent.

Measurements made on rural air samples obtained in southeastern Washington indicated a PERC mixing ratio of 0.020 ± 0.010 ppb (0.13 x 10^{-3} ± 0.07 x 10^{-3} mg/m^{3}) (Grimsrud and Rasmussen, 1975). Analysis was made in a temperature-programmed GC-MS system. Precision difficulties experienced in the PERC measurements were attributed to trace impurities in the carrier gas.

McConnell et al. (1975) has stated that PERC is universally present in ambient air at levels normally in the range of 0.001 to 0.014 ppb.

Pearson and McConnell (1976) found 15 to 40 ppb (0110 to 0.27 mg/m^{3}) in the ambient air in the vicinity of an organochlorine manufacturing site in Great Britain.

In Tokyo, Ohta et al. (1976) concluded from their measurement data that PERC is evenly distributed in the ambient air. Measurements made at 26 geographically selected sites from May 1974 to April 1975 indicated that the annual average mixing ratio was 1.2 ppb (8.1 x 10^{-3} mg/m^{3}). Measurements were made on a gas chromatograph equipped with an electron capture detector. The investigators reported that the analytical error was below 10 percent. During the more recent measurements by Makide et al. (1980), PERC levels at nine rural sites in Japan averaged 0.019 ± 0.010 ppb (0.129 ± 0.068 μg/m^{3}). Analysis was by GC-ECD. Precision was reported to be within 2 percent.

Correia et al. (1977) detected PERC in the ambient air at 29 sites in six countries (Great Britain, The Netherlands, Germany, Belgium, France, and Italy). Mixing ratios ranged from less than 0.01 to 4.72 ppb ($<0.678 \times 10^3$ mg/m^3 to 0.032 mg/m^3). It was judged that quantities found were almost independent of the site of measurement and that PERC is ubiquitous. Ioffe et al. (1977) reported the presence of PERC in the ambient air of Leningrad using GC-MS.

3.6.1.2 Water--Various studies have shown that PERC is found in both natural and municipal waters. A recent review by Deinzer et al. (1978) has summarized many of the findings.

3.6.1.2.1 Natural Waters. Surface waters, such as rivers and lakes, are the most important sources of drinking water in the United States. Attempts have been made to show an epidemiological link between the presence of halogenated organic compounds in drinking water and cancer (Harris and Epstein, 1976).

Dowty et al. (1975) detected PERC by GC-MS techniques in untreated Mississippi River water as well as in treated water. An approximate six-fold reduction in concentration occurred after sedimentation and chlorination. The relative concentration was approximately three times less than trichloroethylene after identical treatment. Tetrachloroethylene in water from a commercial deionizing charcoal filtering unit showed a marked increase over the amount found in finished water from treatment facilities or commercial sources of bottled water. It had the highest relative concentration of 18 compounds identified and was approximately 13-fold higher in concentration than trichloroethylene. The value of charcoal filtering to remove organics from water requires further study.

Suffet et al. (1977) reported detection of PERC in river waters supplying drinking water to Philadelphia, Pennsylvania. The Belmont Water Treatment

Plant, with an average capacity of 78 million gallons per day obtains influent from the Schuykill River.

In a study designed to detect pollutants in surface water at different U.S. sites, Ewing et al. (1977) identified PERC among the pollutants. Detection limits were not reported. The highest level was reported for surface water in Ashtabula, Ohio (45 µg/l), located along the south edge of Lake Erie. In the vicinity of Philadelphia, 3 µg/l was detected. Less than 1 µg/l was reported along the Ohio River and at the confluence of its tributaries. Similarly 1 µg/l or less was reported for all sites sampled in the Great Lakes, and at six sites along the Tennessee River. An exception was Chattanooga where 13 µg/l was reported. In the greater Chicago area, the highest level found was 5 µg/l. In all samples taken in California, Oregon, and Washington, PERC was either not detected or was found at a concentration of 1 µg/l or less. Sampling sites included those in the vicinity of Los Angeles Harbor, Santa Monica Bay and San Francisco Bay, at three sites along the Willamette River in Oregon, and two in the Puget Sound area.

Tetrachloroethylene was among a number of halogenated organics found in community drinking water supply wells in Nassau County, New York. Due to contamination, 16 of these wells were closed by the New York State Health Department (Ewing et al., 1977). The maximum detected level of PERC in the contaminated wells was 375 µg/l. Since PERC is generally not used as a cesspool cleaning agent, previous industrial dumping may be the source of contamination.

Pearson and McConnell (1975) found an average PERC concentration of 0.12 ppb in Liverpool Bay sea water; the maximum concentration found was 2.6 ppb. Sediments from Liverpool Bay were found to contain 4.8 ppb (w/w). No direct correlation was found between PERC concentration in sediments and in the waters above.

Rainwater collected near an organochlorine manufacturing site was found to contain 0.15 ppb (w/w) PERC (Pearson and McConnell, 1975) it was not detected in well waters.

Upland waters of two rivers in Wales were found to contain approximately 0.15 ppb PERC; similar levels of trichloroethylene were found (Pearson and McConnell, 1975).

Löchner (1976) found that levels of PERC in Bavarian lake waters ranged between 0.015 to 3 ppb (0.015×10^{-3} to 2.7×10^{-3} mg/l). European surface waters were reported to have uniform PERC concentrations ranging from 0.2×10^{-3} to 0.002 mg/l. (Dowty et al., 1975).

Analyses of river, canal water, and sea water containing effluent from production and user sites in four countries revealed PERC concentrations ranging from 0.01 to 46 ppb (0.01 to 46 μg/liter) (Correia et al., 1977).

3.6.2.2 Municipal Waters--Bellar (1974) measured the concentration of PERC in water obtained from sewage treatment plants in several cities. Before treatment, the average concentration was 6.2 μg PERC per liter. The treated water before chlorination contained 3.9 μg PERC per liter. After chlorination, the effluent contained 4.2 μg PERC per liter.

Tetrachloroethylene has been detected in the drinking water of a number of U.S. cities. These include: Evansville, Indiana (Keith et al., 1977); Kirkwood, Missouri (Keith et al., 1977); New Orleans, Louisiana (Dowty et al., 1975); Jefferson Parish, Louisiana (Dowty et al., 1975); Cincinnati, Ohio (Keith et al., 1977); Miami, Florida (Keith et al., 1977); Grand Forks, North Dakota (Keith et al., 1977); Lawrence, Kansas (Keith et al., 1977); New York City (Keith et al., 1977); and Tucson, Arizona (Keith et al., 1977).

Concentrations recorded for the above cities were less than 1 μg per liter. An exception was Jefferson Parish, which had a measured concentration of 5 ppb (5 μg/liter). Keith et al. (1977) did not detect PERC in the drinking water of Philadelphia. Tetrachloroethylene was found in Evansville tap water from July 1971 to December 1972. The Ohio River Basin, a heavily industralized area, is upstream from Evansville and serves as a major source of drinking water for that community.

Dowty et al. (1975) determined levels of PERC in the drinking water for New Orleans. Considerable variation in the relative concentrations of the various halogenated compounds was observed from day to day.

Contamination of drinking water by PERC was recently investigated by Wakeham et al., (1980). It was reported that elevated concentrations of PERC were found in drinking water transported in vinyl-coated asbestos-cement pipes in areas of the town of Falmouth, Massachusetts. Tetrachloroethylene is used as a solvent during the application of the vinyl coating to the pipe during manufacture. It was suggested that residual solvent leaches into the water carried in these pipes.

Using a charcoal trap with FID detection, Wakeham and coworkers detected levels ranging from 140 to 18,000 ppb in unflushed pipes. In other parts of the distribution system, levels were less than 2 ppb. The authors reported that vinyl-coated asbestos-cement pipe has been used in parts of the northeastern United States over the past decade in response to concerns that water carried in uncoated pipes could contain asbestos fibers.

In municipal waters supplying the cities of Liverpool, Chester, and Manchester, England, 0.38 ppm (w/w) PERC was found (Pearson and McConnell, 1975).

Munich (Germany) drinking water was analyzed by Löchner (1976). Samples taken at various sampling points and times gave a range of 1.1×10^{-3} to 2.4×10^{-3} mg/liter. Raw sewage at Munich contained 0.088 mg/liter PERC. Upon mechanical clarification the 24-hour average concentration of PERC was 0.0068 mg/liter.

3.7 ANALYTICAL METHODOLOGY

Tetrachloroethylene has been analyzed both in air and in water, as well as in biological fluids, by a variety of methods. Separation of PERC from other compounds is usually carried out by gas chromatography (GC). Quantification is usually made by either electron capture detection (ECD) or mass spectroscopy (MS). These analytical methods, GC/ECD or GC/MS, have a lower limit of detection on the order of a few parts-per-trillion (ppt).

3.7.1 Ambient Air

Because PERC levels in air are typically in the sub-parts-per-billion (ppb) range, the sampling and analysis techniques have been designed to detect trace gas levels.

3.7.1.1 Sampling--Because of the low levels occurring in ambient air, sampling techniques have focused upon adsorption onto solids such as charcoal (Evans et al., 1979) or on concentration methods that increase the amount of PERC to above detection limits (Rasmussen et al., 1977). In the upper troposphere, PERC has been sampled by pumping air into stainless steel or glass containers until there is a positive pressure relative to the surrounding atmosphere (Singh et al., 1979b).

Evans et al. (1979) sampled PERC using a method based on adsorption onto activated charcoal, followed by desorption by carbon disulfide/methanol. The precision of the analytical method, expressed as a coefficient of variation for the total measurement system (including sample collection, handling, and preparation) was reported as 16 percent. When 49 quality control samples were analyzed, the overall percent recovery from the charcoal tubes was 70.2 ± 1.7 percent. When the total measurement system was independently checked by using

Tenax GC, another solid adsorbent, the paired data were correlated with a coefficient of 0.82, with the average Tenax result exceeding the average charcoal result by 21 percent. Samples were in the sub- to low-ppb range. Evans et al. (1979) reported that PERC is stable on charcoal tubes for at least one month at 0°C. The lower limit of detection for the total measurement method (to include gas chromatography/electron capture detection) was estimated at 0.68 $\mu g/m^3$ (0.1 ppb).

Pellizzari and Bunch (1979) reported the use of Tenax GC, a porous polymer based upon 2,6-diphenyl-p-phenylene oxide, to adsorb PERC from ambient air. Recovery was made by thermal desorption and helium purging into a freezeout trap. The estimated detection limit, when high resolution gas chromatography/mass spectrometry is used, is 0.38 ppt (2.5×10^{-6} mg/m^3). Accuracy of analysis was reported at ± 30 percent. Included among the inherent analytical errors were (1) the ability to accurately determine the breakthrough volume, (2) the percent recovery from the sampling cartridge after a period of storage, and (3) the reproducibility of thermal desorption from the cartridge and its introduction into the analytical system. To minimize loss of sample, cartridge samplers should be enclosed in cartridge holders and placed in a second container that can be sealed, protected from light, and stored at 0°C. The advantages reported for Tenax include (1) a low water retention, (2) a high thermal stability, and (3) low background levels (Pellizzari, 1974; Pellizzari, 1975; Pellizzari, 1977; Pellizzari et al., 1976).

Knoll et al (1979) reported resolution of PERC from other chlorinated hydrocarbons with Carbopak C-HT, a graphitized thermal carbon black treated with hydrogen at 1,000°C. Carbowax 20M, reacted with nitroterephthalic acid, was reported not to give good separation. Porapak T, a porous polymer based on ethylene glycol dimethacrylate, was reported to give good separation.

A freeze-out concentration has been developed by Rasmussen and coworkers (1977) to determine trace levels of PERC in the presence of other compounds. The detection limit was reported at 0.2 ppt (1.36×10^{-6} mg/m^3) for 500 ml aliquots of ambient air samples measured by gas chromatography coupled with electron capture detection. When freeze-out is complete, PERC remains behind while such gases as oxygen and nitrogen are passed through as the freeze-out loop is heated. The carrier gas sweeps the contents onto the column.

Singh et al. (1979a) have employed the cryogenic trapping of air containing trace levels of PERC and other compounds of interest. During sampling, traps are maintained at liquid oxygen temperature. Traps were made of stainless steel packed with a 4-inch bed of glass beads or glass wool. Aliquots are thermally desorbed and injected directly into the gas chromatograph. Both electric heating and hot water desorption techniques were found to be satisfactory.

Makide et al. (1980) employed stainless steel canisters for sampling of air containing PERC at levels of about 20 ppt. Canisters were polished electrochemically. Canisters were evaluated to 10^{-4} Pa at 200°C prior to sampling. The composition of the samples were reported to have remained unchanged for over a year.

The monitoring method recommended by the National Institute for Occupational Safety and Health (1977) utilizes adsorption on charcoal followed by desorption with carbon disulfide. This method is recommended for the range 96 to 405 ppm (655 to 2,749 mg/m^3). The coefficient of variation for the analytical and sampling method is 0.052. A reported disadvantage is that the charcoal may be overloaded, thus limiting the amount of sample that can be collected.

Budde and Eichelberger (1979) reported that carbon adsorption methods, in general, have more disadvantages than those methods using porous polymers. The advantage of porous polymers coupled with thermal desorption, as contrasted with solvent desorption, is higher sensitivity because the total sample is measured and there is no background from the solvent. However, since the total sample is measured, multiple samples must be collected to insure against accident, loss of sample, and to obtain information on the precision of the method. Tenax GC was reported to be superior to other polymers for organics analysis. Samples are taken by pulling air through glass tubes packed with Tenax GC, 60/80 mesh and supported by plugs of glass wool. After a suitable sampling period (about 2 to 4 hours in urban areas), tubes are capped and stored. Samples are thermally desorbed (250 to 270°C) for 3 minutes under a 10 ml helium flow.

Criteria to evaluate methods using solid sorbents to collect organic compounds from air have been discussed by Melcher et al. (1978). Among the factors to be considered are effects of (1) size of collection tube (2) breakthrough volume, (3) humidity, (4) temperature, (5) migration, (6) desorption efficiency, and (7) concentration.

3.7.1.2 Analysis--The sampling methods which use solid adsorbents or cryogenic techniques have the trap connected to the gas chromatograph by multiple-port gas sampling valves. With solid traps, the collected organics are quickly heated and the desorbed organics are passed through capillary columns. A number of coating materials in the capillary columns have been successfully used for separating PERC. These materials include: (1) SF-96 on 100/120 mesh Chromosorb W (Cronn et al.,1977); (2) SP-2100 on 80/100 mesh Supelcoport (Singh et al., 1979); (3) 80/100 mesh Carbopak C-HT, Porapak T, and SP-2100/0.1 percent Carbowax 1500 on 100/ 120 mesh Supelcoport (Knoll et al., 1979). In the method used by Evans et al. (1979) in field studies, a 1.8 meter glass column with a 2-mm i.d., packed with 0.1 percent SP-1000 on Carbopack C, 80/100 mesh was used to separate PERC from other organics in ambient air samples. Twenty four-hour samples were adsorbed onto charcoal. After desorption with carbon disulfide/methanol, a 1.0-μl aliquot is injected into the gas chromatograph. The separation conditions included an oven temperature of 125°C (all transfer lines at least 170°C) and the carrier gas was 5 percent methane in argon. Quantification was made by ECD (Nickel 63; ECD temperature of 218°C) and a standing current of 0.5 amperes. To insure that the cell was not contaminated, the sensitivity of the detector was evaluated by comparing the standing current with the pulse frequency curve.

Electron capture detection is a method of choice used by a number of investigators (Singh et al., 1979; Rasmussen et al., 1977; Singh et al., 1977). Singh et al. (1979) maintained the ECD at a higher temperature (325°C) than that used by Evans et al. (1979) because it was found that the ECD response increased with an increase in temperature. The identity of PERC was confirmed by determining its ionization efficiency as well as the EC thermal response.

Using two ECD's in series, Lillian and Singh (1974) determined the ionization efficiency to be 70 percent. Once known for the GC-ECD operating conditions, the ionization efficiency can be used to calculate the amount of PERC in a sample coulometrically, according to the equation:

$$\text{coulombs} = 96{,}400\ pQ$$

where p = ionization efficiency, and

Q = moles of compound.

Lillian and Singh (1974) reported that the accuracy associated with GC-ECD measurements of compounds having ionization efficiencies exceeding 50 percent is 75 percent or greater. In a comparison of GC-ECD with GC-MS, Cronn et al.,

(1976) judged GC-ECD to be superior in reproducibility for quantitating halocarbons. Of four halocarbon standards (PERC not among them) measured by GC-ECD, the coefficients of variation ranged from 1.4 to 4.3 percent, compared to a range of 4 to 19 percent when 11 halocarbon standards were measured by GC-MS.

A close agreement between the levels of PERC and other halocarbons determined by GC-ECD and GC-MS, on the same ambient air samples, was obtained by Russell and Shadoff (1977).

GC-ECD was used by Pellizzari et al. (1979b) to measure PERC in ambient air samples. Samples were adsorbed onto charcoal, desorbed with a mixture of methanol and carbon disulfide and aliquots were separated on a 2.5-mm (i.d.) Pyrex column containing 0.2 percent Carbowax 1500 on Carbopack C. The estimated detection limit was 2.5×10^{-6} mg/m^3 (0.38 ppt).

Makide et al. (1980) separated trace levels of PERC from other halogenated organics on a silicone OV-101 column (10 percent by weight coated on Chromosorb W-HP, 80-100 mesh), 5 mm i.d. and 3 meters long. Samples were transferred to the column cooled at -40°C during preconcentration. Separation was carried out by raising column temperature 5°C per minute up to 70°C. Methane was added to the carrier gas (nitrogen) to improve the signal-to-noise ratio and to stabilize the baseline. Quantification was made by a constant current ECD. The detection limit for PERC was reported as <0.05 ppt. Precision was reported to be within 2 percent.

To measure PERC at levels expected to occur in occupational air, flame ionization detection has been used. The analytical method S335, suggested by NIOSH (11) for organic solvents in air utilizes adsorption onto charcoal, followed by desorption with carbon disulfide. PERC is separated by gas chromatography. The method is recommended for the range 96 to 405 ppm (655 to 2,749

mg/m^3). The coefficient of variation for the analytical and sampling method is 5.2 percent. With the method, interferences are minimal and those that do occur can be eliminated by altering chromatographic conditions.

3.7.2 Water

3.7.2.1 Sampling--A variety of techniques and methods are commonly used to sample trace levels of PERC and other halogenated organics in water samples.

3.7.2.1.1 Gas purging and trapping. In this method, finely divided gas bubbles are passed through the sample, transferring the organic compounds to the gas phase. The gas is then passed through a solid adsorbent in a trap. Compounds are desorbed at elevated temperature by backflushing with a carrier gas into the gas chromatograph (Budde and Eichelberger, 1979). Since the boiling point of PERC is 121°C, Tenax GC would be an effective absorbent.

The purge and trap procedure is widely used, as is the purging device developed by Bellar and Lichtenberg (1974). For most organic compounds, detection limits as low as 1 μg/l can be obtained when gas chromatography/mass spectroscopy is used for analysis. Mieure (1980) reported that adding salt to or increasing the temperature of the sample dramatically improves the removal of most organic compounds.

3.7.2.1.2 Headspace analysis. This method describes static sampling of the vapor phase that is in equilibrium with the aqueous sample. The concentration in the headspace is proportional to the concentration in the water (Kepner et al., 1964). In this procedure, trace organics in the range of 10 to 100 μg/l can be sampled (Mieure, 1980). Mieure (1980) reported a detection limit for PERC (analyzed by electron capture detection) of 0.01 μg/l. With flame ionization detection, the limit was 32 μg/l. Typically, a 1- to 2-ml sample of the headspace is removed and injected into the gas chromatograph.

3.7.2.1.3 Liquid/liquid extraction. Mieure (1980) reported that recovery of PERC from water spiked with from 2.3 to 90 μg/l ranges from 100 to 113 percent. The precision ranges from 10 to 12 (RSD). These results were obtained from a round-robin study, by the ASTM Committee D19 on Water, using liquid/liquid extraction. The extractant was not identified.

Budde and Eichelberger (1979) cautioned that a disadvantage is that very volatile compounds may be lost during extract concentration or during solvent elution from the gas chromatograph. Methylene chloride was recommended as the only general purpose solvent.

Sheldon and Hites (1978) used methylene chloride in a sampling procedure applied to the identification of PERC and 98 other organic compounds in river water. Grab samples were collected in amber glass bottles and samples for solvent extraction were immediately preserved by acidifying to pH 2 with hydrochloric acid and by adding 250 ml of methylene chloride. The analytical techniques used were those reported by Jungclaus et al. (1978). Solvent extraction efficiencies were not determined. While PERC was previously detected in vapor stripping analysis of prior samples, it was not detected in the water samples cited in their report.

3.7.2.2 Analysis--Schwarzenbach et al. (1979) used ECD to measure PERC levels in water samples. Volatile organics were purged, adsorbed onto charcoal. Desorption was by carbon disulfide. Quantification was made by FID and ECD.

Dowty et al. (1975) used Tenax GC in trapping purgeable organics from water samples. The polymer containing the trapped organics was placed in the GC injection port maintained at 200°C. Final separation was made on a glass capillary column coated with Pluronics 121. The effluent of the column was split to allow for FID and ECD.

3.7.3 Calibration

Singh et al. (1977d) reported that multiple dilution of pure materials at ppt levels is tedious and inaccurate; surface sorption and heterogenous reactions are predominant factors leading to inaccuracies. Permeation tubes, while satisfactory for many halocarbons in establishing primary standards, were judged unsatisfactory for PERC. The permeation rate at the 95 percent confidence limit was 64.8 ± 26.1 ng/min. While PERC permeation tubes were observed to perform satisfactorily for short time periods, errors of less than 10 percent were difficult to obtain.

3.7.4 Storage of Vapors Containing PERC

Sampling of exhaled breath commonly is accomplished by use of Saran bags or glass pipettes. Temperature and storage time before analysis are factors to be considered in obtaining accurate data.

3.7.4.1 Glass Sampling Tubes--Evaluation of glass sampling tubes was made by Pasquini (1978). Serial alveolar breath samples were collected in the tubes and the concentrations of PERC analyzed by a gas chromatograph equipped with a flame ionization detector. Analysis of vapor retention over 169 hours indicated that glass tubes can be acceptable containers for breath samples if precautions are taken. Moisture, temperature, and tube surface and condition can greatly alter vapor retention.

In tubes filled with breath samples taken at room temperature and also stored at room temperature, the mean percent loss of PERC was 64.8 ± 9.4. Partitioning of PERC between the vapor and liquid states appears to be a reasonable explanation to account for vapor retention loss. It was shown for trichloroethylene that if storage tubes were maintained at 37°C, vapor retention was greater. It was also greater if siliconized tubes were used.

3.7.4.2 Saran®, Teflon® and Tedlar® Containers--Saran® bags as storage containers for PERC vapors have been evaluated by Desbaumes and Imhoff (1971). Although it was concluded that Saran® can be an acceptable container, the diffusion rate was appreciable over a 24-hour storage period. Storage temperature was not reported.

Teflon® containers were judged by Drasche et al. (1972) to be more suitable than Saran® even though losses of PERC due to adherence to Teflon® surfaces were appreciable. Within the first 30 minutes after introduction of a mixture (relative humidity = 45 percent) of benzene, trichloroethylene, and PERC into a Teflon® bag, vapor concentrations of each dropped 40 to 60 percent. However, upon heating the bag to 100°C for 30 minutes after the mixture had been stored for 44 hours at 25°C, concentrations rose to the initial values.

Knoll et al. (1979) reported that PERC, when stored at ambient temperatures for 10 days or less in Tedlar® bags, was stable. When the vapor mixture is heated to 70°C, PERC is stable for no more than 5 hours.

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4. ECOSYSTEM CONSIDERATIONS

4.1 EFFECTS ON AQUATIC ORGANISMS AND PLANTS

Tetrachloroethylene (PERC) has been tested for acute toxicity in a limited number of aquatic species. The information presented in this chapter presents observed levels that were reported to result in adverse effects under laboratory conditions. It is recognized that such parameters of toxicity are not easily extrapolated to environmental situations. Test populations themselves may not be representative of the entire species in which susceptibility of various lifestages to the test substance may vary considerably.

Guidelines for the utilization of these data in the development of criteria levels for PERC in water are discussed elsewhere (USEPA, 1979).

The toxicity of PERC to fish and other aquatic organisms has been gauged principally by flow-through and static testing methods (USEPA, 1975). The flow-through method exposes the organism(s) continuously to a constant concentration of PERC while oxygen is continuously replenished and waste products are removed. A static test, on the other hand, exposes the organism(s) to the added initial concentration only. Both types of tests are commonly used as initial indicators of the potential of substances to cause adverse effects.

4.1.1 Effects on Freshwater Species

Alexander et al. (1978) used both flow-through (measured) and static (unmeasured) methods to investigate the acute toxicity of several chlorinated solvents, including PERC, to adult fathead minnows (*Pimephales promelas*). Studies were conducted in accordance with test methods described by the U.S. Environmental Protection Agency (USEPA, 1975).

The static and flow-through results for the 96-hour experiments indicated that PERC was the most toxic of the solvents tested. The lethal concentration (96-hour LC50) necessary to kill 50 percent of the fathead minnows in the flow-through test was 18.4 mg/liter (18.4 ppm); the 95 percent confidence limits were 14.8 to 21.3 mg/liter (14.8 to 21.3 ppm). In comparison, the static experiments gave a 96-hour LC50 of 21.4 mg/liter (21.4 ppm); the 95 percent confidence limits were 16.5 to 26.4 mg/liter (16.5 to 26.4 ppm).

When the minnows were exposed to sublethal levels for short exposure intervals, only reversible effects were observed. Endpoints evaluated were loss of equilibrium, melanization, narcosis, and swollen hemorrhaging gills. The effective concentration (EC50) of PERC that produced one or more of these reversible effects was 14.4 mg/liter (14.4 ppm).

The 96-hour LC50 in a static test with the bluegill (Lepomis macrochirus) was reported as 12.9 mg/liter (12.9 ppm) (USEPA, 1978,1980)

In comparing the 96-hour LC50 values for other chlorinated compounds with bluegill, it is suggestive that toxicity increases with an increase in chlorination of the compounds (USEPA, 1980).

The most sensitive species tested is the rainbow trout (Salmo gairdneri). The LC50 determined by a flow through measured procedure was 5.28 mg/l (5.28 ppm) (USEPA, 1980).

With embryo-larval test procedures, a chronic value of 0.840 mg/l (0.840 ppm) was obtained by the USEPA (1980) for the fathead minnow.

With the freshwater invertebrate, Daphnia magna, a 48-hour EC50 value of 17.7 mg/l (17.7 ppm) was obtained (USEPA, 1980). The midge, Tanytarsus dissimilis, was more resistant, with a 48-hour LC50 value of 30.84 mg/l (30-84 ppm), determined under static measured conditions.

4.1.2 Effects on Aquatic Plants

As cited in the USEPA Ambient Water Quality Criteria Document (USEPA, 1980), no adverse effects on chlorophyll *a* or cell numbers of the freshwater alge, *Selenastrum capricornutum*, were observed at exposure concentrations as high as 816 mg/l (816 ppm).

For the saltwater species, *skeletonema costatum*, a 96-hour EC50 of about 500 mg/l (500 ppm) was determined for effects on chlorophyll *a* and cell number. This alga species is more resistant than the alge, *Phaeodactylum tricornutum* for which the EC50 value was determined to be 10.5 mg/l (10 ppm) (Pearson and McConnell, 1975).

4.1.3 Effects on Saltwater Species

Pearson and McConnell (1975) investigated the acute toxicity of PERC on the dab (*Limanda limanda*), barnacle larvae (*Barnacle nauplii*), and on unicellular algae (*Phaeodactylum tricornutum*). The LC50 was 5 mg/liter (5 ppm) for the dab. The 48-hour LC50 for barnacle larvae was 3.5 mg/liter (3.5 ppm).

Toxicity to the unicellular algae was assessed by measuring alterations in the uptake of carbon from atmospheric carbon dioxide during photosynthesis. Uptake of carbon dioxide was measured by the use of sodium-^{14}C-carbonate. The EC50 was 10.5 mg/liter (10.5 ppm).

Data collected by the U.S. Environmental Protection Agency (1980) indicate that for mysid shrimp (*Mysidopsis bahia*) the LC50 was 10.2 mg/liter (10.2 ppm) in a 96-hour static, unmeasured procedure. Chronic testing over the life cycle of the mysid shrimp resulted in a chronic value of 0.450 mg/liter (0.45 ppm) (USEPA, 1980).

4.2 BIOCONCENTRATION AND BIOACCUMULATION

An indicator of the potential for a substance to result in cumulative or chronic toxic effects in aquatic species is the bioconcentration factor (BCF).

Bioconcentration refers to the increased concentration of a substance within an organism (e.g. fish) relative to the ambient water concentration under steady-state conditions. As defined by Veith et al. (1979), the bioconcentration factor is a constant of proportionality between the concentration of the chemical in fish and in the water. Bioaccumulation, a term often erroneously used in place of bioconcentration, can be defined as that process which includes bioconcentration and any uptake of toxic substances through consumption of one organism by another. The BCF alone, however, may not be the most useful measure of the overall fate of a substance in water or its potential for producing toxic effects. Chemical and biological degradation of the substance, volatilization, desorption and the depuration rate are among the key determinants of toxicity.

A measure commonly used to assess the degree to which a compound may be bioconcentrated in the absence of direct measurement is the octanol-water partition coefficient. In guidelines recently set forth by the American Society for Testing and Materials (ASTM), a log partition coefficient exceeding a value of three was considered an indication of a high probability of measurable bioaccumulation in aquatic species (ASTM, 1978). Compounds that exhibit a large log coefficient generally are those with low water solubility and high solubility in organic solvents. Although a compound may demonstrate a high BCF or log partition coefficient, other environmental factors that act to reduce this potential often exist. The compound may be rapidly hydrolyzed or be degraded by other mechanisms. Measurable uptake by the organism may be precluded if the tissue depuration rate for the substance is great.

With regard to PERC, the BCF was calculated to be 34 and 49, in two fish species (USEPA, 1980; Neely et al., 1974). Neely et al. (1974) found that the BCF for PERC and other chemicals was linearly related to the respective partition coefficients. For PERC the log partition coefficient was 2.88 and the BCF, determined in trout (rainbow) muscle, was 39.6 ± 5.5. The trout were exposed to two undefined levels of PERC for an undefined period of time. The extent to which the levels approached the acute LC50 level for this species or whether a steady-state was achieved was not reported. Preliminary data in the U.S. Environmental Protection Agency study (1980) with bluegill, indicated a BCF of 49. The log partition coefficient was 2.53. The depuration rate was rapid with a half-life of less than one day.

Although these studies suggest that PERC does have bioconcentration potential, the extent to which this potential can be manifested in the form of adverse effects can be only gauged from the results of toxicological studies.

4.2.1 Levels of Tetrachloroethylene in Tissues of Aquatic Species

Pearson and McConnell (1975) suggested that chronic and sublethal effects of PERC may result from exposure to low concentrations of PERC if the halocarbon can be bioaccumulated. As a first step in addressing the question of bioaccumulation, these investigators determined levels of PERC in a variety of invertebrate and vertebrate species (Tables 4-1 and 4-2).

Among marine invertebrates, wet tissue concentrations of PERC were found to range from 0.001 to 0.009 ppm. The highest concentration (0.008 to 0.009 ppm) found was in the crab (Cancer pagurus). Higher levels were found in marine algae (0.013 to 0.022 ppm). In tissues of fish, a range of 0.0003 to 0.041 ppm was found. Concentrations in the livers of three species of fish were found to greatly exceed those found in the flesh. Tissue levels from all species are shown in Table 4-1.

The average concentration of PERC in seawater taken from Liverpool Bay, an area where many species of organisms were collected, was 0.00012 ppm. A comparison of this value with those presented in Table 7-1 indicate

TABLE 4-1. LEVELS OF TETRACHLOROETHYLENE IN TISSUES OF MARINE ORGANISMS, BIRDS AND MAMMALS (Pearson and McConnell, 1975)

Species	Source	Tissue	Trichloro-ethylene[a] ppm x 10^3	PERC ppm x 10^3
Invertebrates				
Plankton	Liverpool Bay	-	0.05 - 0.4	0.05 - 0.5
Plankton	Torbay	-	0.9	2.3
Ragworm (Nereis diversicolor)	Mersey Estuary	-	Not detected	2.9
Mussel (Mytilus edulis)	Liverpool Bay	-	4 - 11.9	1.3 - 6.4
	Firth of Forth	-	9	9
	Thames Estuary	-	8	1
Cockle (Cerastoderma edule)	Liverpool Bay	-	6 - 11	2 - 3
Oyster (Ostrea edulis)	Thames Estuary	-	2	0.5
Whelk (Buccinum undatum)	Thames Estuary	-	Not detected	1
Slipper limpet (Crepidula formicata)	Thames Estuary	-	9	2
Crab (Cancer pagurus)	Tees Bay	-	2.6	2.3
	Liverpoool Bay	-	10 - 12	8 - 9
	Firth of Forth	-	15	7
Shorecrab (Carcinus maenus)	Firth of Forth	-	12	6
Hermit crab (Eupagurus bernhardus)	Firth of Forth	-	15	15
	Thames Estuary	-	5	2
Shrimp (Crangon crangon)	Firth of Forth	-	16	3

(continued)

TABLE 4-1. (continued)

Species	Source	Tissue	Trichloroethylene[a] ppm x 10^3	PERC ppm x 10^3
Starfish (*Asterias rubens*)	Thames Estuary	-	5	1
Sunstar (*Solaster sp.*)	Thames Estuary	-	2	2
Sea Urchin (*Echinus esculentus*)	Thames Estuary	-	1	1
Marine Algae				
Enteromorpha compressa	Mersey Estuary	-	19 - 20	14 - 14.5
Ulva lactuca	Mersey Estuary	-	23	22
Fucus vesiculosus	Mersey Estuary	-	17 - 18	13 - 20
Fuscus spiralis	Mersey Estuary	-	16	13
Fish				
Ray (*Raja clavata*)	Liverpool Bay	flesh	0.8 - 5	0.3 - 8
		liver	5 - 56	14 - 41
Plaice (*Pleuronectes platessa*)	Liverpool Bay	flesh	0.8 - 8	4 - 8
		liver	16 - 20	11 - 28
Flounder (*Platyethys flesus*)	Liverpool Bay	flesh	3	2
		liver	2	1
Dab (*Limanda limanda*)	Liverpool Bay	flesh	3 - 5	1.5 - 11
		liver	12 - 21	15 - 30
Mackerel (*Scomber scombrus*)	Liverpool Bay	flesh	5	1
		liver	8	not detected

(continued)

TABLE 4-1. (continued)

Species	Source	Tissue	Trichloroethylene^a ppm x 10^3	PERC ppm x 10^3
Dab (*Limanda limanda*)	Redcar, Yorks	flesh	4.6	5.1
Plaice (*Pleuronectes platessa*)	Thames Estuary	flesh	2	3
	Thames Estuary	flesh	3	3
Sole (*Solea solea*)	Thames Estuary	flesh	2	4
		suts	11	1
Redgurnard (*Aspitnigla cuculus*)	Thames Estuary	flesh	11	1
		suts	6	2
Scad (*Trachurus trachurus*)	Thames Estuary	flesh	2	4
Pout (*Trisopterus luscus*)	Thames Estuary	flesh	2	2
Spurdog (*Squalus acanthias*)	Thames Estuary	flesh	3	1
Mackerel (*Scomber scombrus*)	Torbay, Devon	flesh	2.1	Not detected
Clupea sprattus	Torbay, Devon	flesh	3.4	1.6
Cod (*Gadus morrhua*)	Torbay, Devon	flesh	0.8	<0.1
		Air bladder	<0.1	3.6
Sea and Freshwater Birds				
Gannet (*Sula bassana*)	Irish Sea	liver	4.5 - 6	1.5 - 3.2
		eggs	9 - 17	4.5 - 26
Shag (*Phalacrocerax aristotelis*)	Irish Sea	eggs	2.4	1.4
Razorbill (*Aka torda*)	Irish Sea	eggs	28 - 29	32 - 39

(continued)

TABLE 4-1. (continued)

Species	Source	Tissue	Trichloro-ethylene[a] ppm x 10^3	PERC ppm x 10^3
Kittiwake (*Rissa tridactyla*)	North Sea	eggs	33	25
Swan (*Cygnus olor*)	Frodsham Marsh	liver	2.1	1.9
		kidney	14	6.4
Moorhen (*Gallinula chloropus*)	Merseyside	liver	6	3.1
		muscle	2.5	0.7
		eggs	6.2 - 7.8	1.3 - 2.5
Mallard (*Anas platyrynchos*)	Merseyside	eggs	9.8 - 16	1.9 - 4.5
Mammals				
Grey Seal (*Halichoerus grypus*	Farne Island	blubber	2.5 - 7.2	0.6 - 19
		liver	3 - 6.2	0 - 3.2
Common Shrew (*Sorex araneus*)	Frodsham Marsh	-	2.6 - 7.8	1

[a] Levels for trichloroethylene included for comparative purposes.

TABLE 4-2. ACCUMULATION OF TETRACHLOROETHYLENE BY DABS (Pearson and McConnell, 1975)

Tissue	Period of Exposure (days)	Mean Exposure Concentration (ppm	Mean Concentration in Tissue (ppm x 10^3)	Accumulation Factor
flesh	3 - 35	0.3	2,800[a] (13)	x 9
liver	3 - 35	0.3	113,000 (14)	x 400
flesh	3 - 35	0.03	160 (9)	x 5
liver	3 - 35	0.03	7,400[b] (9)	x 200
flesh	10	0.2	1,300 (7)	x 6
liver	10	0.2	69,000 (7)	x 350

Numbers in parentheses are number of specimens analyzed.

[a] One fish had a flesh concentration of 29.7 ppm and was omitted from calculations.

[b] One fish had flesh concentration of 50.3 ppm and was omitted from calculations.

an uptake as much as 75-fold. It was the authors' contention that, based on their observations, there is little indication that bioaccumulation occurs in the food chain.

As shown in Table 4-2, dabs (Limanda limanda) exposed to 0.3 ppm for 3 to 35 days were found to have a BCF (liver) for PERC of 400. It was not reported whether this period of exposure approximated a steady-state for PERC. After dabs were returned to clean seawater, the level of PERC dropped to 1/100 of the original level in 4 days and to 1/1000 of the initial level after 11 days (Figure 4-1). The ratio between liver and flesh concentrations is approximately 100 to 1. The relationship between flesh and liver concentrations in the dab is shown in Figure 4-2.

Dickson and Riley (1976) detected PERC in three species of mollusks and in five species of fish collected near Port Erin, Isle of Man. Levels of PERC

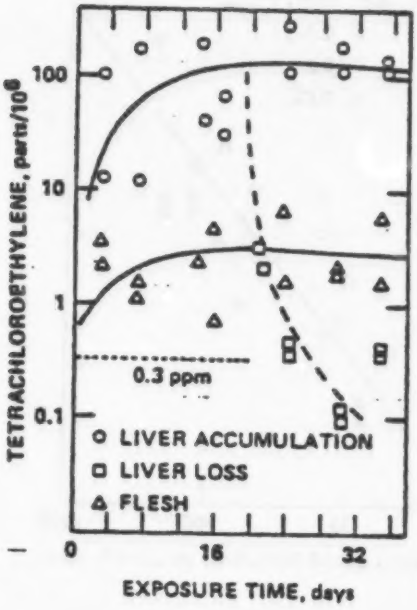

Figure 4-1. Accumulation and loss of tetrachloroethylene by dabs (Alexander et al., 1978).

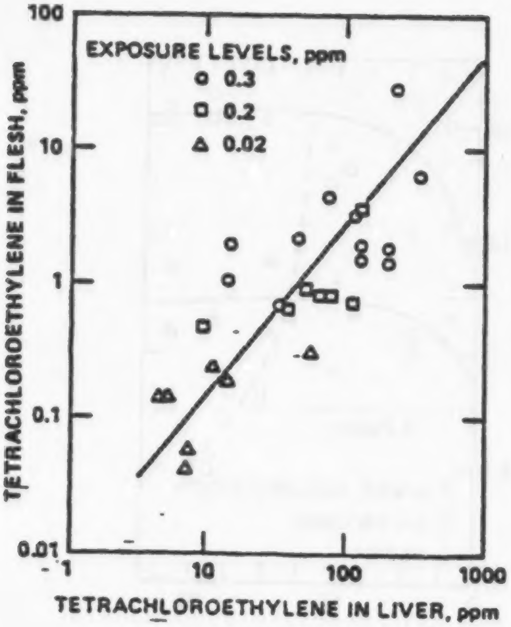

Figure 4-2. Relation between flesh and liver concentrations of tetrachloroethylene in dabs (Alexander et al., 1978).

in various tissues are shown in Table 4-3. Relative to the PERC concentration in seawater, there was only a slight enrichment in the tissues (<25 times). Tetrachloroethylene had one of the lowest mean bioconcentration factors. In contrast, the analog trichloroethylene had the highest mean bioconcentration factor.

4.3 BEHAVIOR IN WATER AND SOIL

The potential of any substance for bioconcentration is influenced by many factors, including the rate at which it volatizes and its reactivity.

In the laboratory study by Dilling et al. (1975). The measured half-life of PERC was from 24 to 28 minutes in water. Factors affecting the evaporation of PERC were surface wind speed, agitation of the water, and water and air temperatures. Reactivity of PERC in water was measured by exposing sealed quartz tubes containing 1 ppm PERC to sunlight for one year. At six months, the level of PERC had declined to 0.52 ppm and at one year, to 0.25 ppm.

The field studies of Zoeteman et al. (1980) suggest that PERC is more persisent in natural water environments than is indicated by laboratory measurements. In a field study of the persistence of a variety of organic chemicals in different aquatic environments in the Netherlands, Zoeteman et al. (1980) estimated the persistence of PERC in river water from 3 to 30 days (half-life). In lakes and groundwaters, the half-life was estimated at 10 fold higher. Estimates were derived from monitored values of samples collected between two sites along the Rhine River, into which no discharges were expected. PERC was analyzed by GC-MS.

TABLE 4-3. CONCENTRATION OF PERC AND TRICHLOROETHYLENE IN MOLLUSKS AND FISH NEAR THE ISLE OF MAN (Dickson and Riley, 1976)

Species	mg x 10^6/g dry weight tissue PERC	 TRICHLOROETHYLENE
Eel (Conger conger)		
brain	6	62
gill	2	29
gut	3	29
liver	43	43
muscle	1	70
Cod (Gadus morhua)		
brain	3	56
gill	-	21
heart	3	11
liver	8	66
muscle	2	8
skeletal tissue	-	-
stomach	6	7
Coalfish (Pollachius birens)		
alimentary canal	-	306
brain	-	71
gill	4	-
heart	-	-
liver	6	70
muscle	2	8

(continued)

TABLE 4-3. (continued)

Species	mg x 10^6/g dry weight tissue PERC	TRICHLOROETHYLENE
Dogfish (Scylliorhinus canicula)		
brain	12	40
gill	13	176
gut	-	41
heart	-	274
liver	9	479
muscle	-	41
spleen	-	307
Bib (Trisopterus luscus)		
brain	-	-
gill	27	40
gut	4	-
liver	0.3	143
muscle	-	187
skeletal tissue	-	185
Baccinum undatum		
digestive gland	33	2
muscle	39	-
Modiolus modiolus		
digestive tissue	-	56
mantle	63	250
muscle	16	33
Pecten maximus		
gill	88	detected
mantle	40	-
muscle	24	-
ovary	-	-
testis	176	-

Estimates of the persistence of PERC in rivers, lakes, and ponds, by calculation according to Smith et al. (1980), are in general agreement with the field results of Zoeteman and coworkers (1980). The half-life of PERC is obtained from the expression:

$$t\ 1/2 = \frac{0.693}{k_v^c}$$

where k_v^c is the volatilization rate constant.

Using the data provided by Smith et al. (1980), the t 1/2 (days) is as follows: ponds, 9 to 20; lakes, < 1 to 20; rivers, <1 to 20.

Bouwer et al. (1981) found that PERC and other halogenated organics have the potential to leach rapidly through soil. When secondary treated municipal wastewater containing from 1 to 10 ng/l PERC was applied to soil columns, at rates typical of high-rate land application systems and under conditions in which volatilization was prevented, PERC was detected in the effluent.

Leaching of PERC through soil was suggested by Zoeteman et al. (1980) as a probable factor in the contamination of groundwater supplies in the Netherlands.

The potential for halogenated organics, including PERC, to contaminate groundwater supplies via leaching from surface waters was examined by Scwarzenbach and Westall (1981). In batch and columns experiments with various types of sorbents and organics, designed to simulate field conditions, these investigators found that the partition coefficient for a particular compound can be estimated from its octanol/water partition coefficient and from the fraction of organic carbon in the sorbent. A high degree of correlation was found between the partition coefficient and organic carbon content when the fraction of organic carbon was greater than 0.1 percent. A partition coefficient of 0.56 ± 0.09 was found for PERC, using natural aquifer material (organic carbon = 0.15 percent) a field site in Switzerland. It was concluded that, for concentrations typically encountered in natural waters, sorption of PERC and other organics of comparable lipophilicity by aquifer materials is reversible. The expression:

$$S = k_pC$$

Where, S = concentration in solid phase

kp = partition coefficient

C = concentration in liquid phase

was found satisfactory to describe sorption equilibrium.

4.4 SUMMARY

The available data for PERC indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 5,280 and 840 μg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

For saltwater aquatic life, the acute and chronic toxicity values are 10,200 and 450 μg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Contamination of groundwater supplies by PERC leaching through soil can be a problem of serious concern, particularly involving soils of low organic carbon content.

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5. COMPOUND DISTRIBUTION AND RELATED PHARMACOKINETICS

5.1 HUMAN AND ANIMAL STUDIES

5.1.1 Absorption

5.1.1.1 Pulmonary--Inhalation is the principal route by which tetrachloroethylene (PERC) enters the body. During inhalation, PERC is absorbed by the blood via alveolar air. Approaches used in calculating the amount absorbed are principally those involving serial breath analysis, i.e., measuring the amount exhaled.

In serial determinations of PERC in alveolar breath and in blood, during and following exposure of males and females to 25, 50, 100, and 150 ppm (170, 339, 678, and 1,017 mg/m^3), Stewart and coworkers (Hake et al., 1976) concluded that the compound was rapidly absorbed. The amount absorbed at a given vapor concentration (exposure periods were 1.3, 5.5, and 7.5 hours per day with samples collected 8 to 24 hours after exposure) was reported to be directly related to the respiratory minute volume. The minute volume is defined as the product of the tidal volume and the respiratory frequency over a 1-minute period.

Absorption of PERC at levels exceeding about 70 ppm (475 mg/m^3) by the lungs was reported to decrease with continuation of exposure ($p < 0.05$); approximately 25 percent less was absorbed in the fourth hour as compared with the first hour of exposure. In this study by Monster et al. (1979), six male volunteers were exposed in a chamber for 4 hours to 72 ± 2 ppm (488 ± 13 mg/m^3) and to 144 ± 7 ppm (977 ± 47 mg/m^3) while at rest. The effects of a workload (bicycle ergometer) were determined in a separate exposure of the volunteers to 142 ± 6 ppm (963 ± 41 mg/m^3); individuals exercised for two 30-minute periods during the 4-hour exposure period.

There was a 2-week interval between each exposure mode. During each mode, the individuals inhaled vapors through a gas mask and exhalations were made into a Tedlar® bag.

The total uptake, shown in Table 5-1, was dependent on both lean body weight (coefficient of variation = 11 percent) and adipose tissue. Uptake is defined as the amount of PERC absorbed per minute. The inter-individual coefficient of variation of body burden predicted by measurements of PERC in exhaled air or in blood was about 25 percent. The individual uptake at 144 ppm (977 mg/m^3) was 2.1 times higher than at 72 ppm (488 mg/m^3) when individuals were at rest. During exercise, total uptake increased about 40 percent; exercise had no effect on the half-life of elimination or on the rate constant of elimination. Minute volume was three-fold higher than that observed when the individuals were at rest. An alveolar retention of approximately 60 percent was calculated at the end of the 4-hour exposure period. Alveolar retention is defined as the percentage difference between the amount inhaled and the amount exhaled.

Monster (1979) suggested that the decrease in absorption (declining lung clearance) upon continuing exposure reflected the small degree to which PERC was metabolized, in contrast to trichloroethylene which has a more constant rate of absorption but is metabolized to a much greater degree. It should be noted, however, that chronic exposure to environmental levels of PERC, (generally less than 10 ppb in ambient air) may not follows the patterns of absorption and lung clearance observed by Monster and coworkers.

5.1.1.2 Percutaneous--Absorption of PERC through the skin is, under most circumstances of use, of minor consideration. Stewart and Dodd (1964) observed absorption in each of five individuals after one thumb of each was immersed in a beaker of PERC, located in a ventilated hood. By measuring concentrations in alveolar breath samples, the investigators concluded that there is little likelihood that toxic amounts of PERC will be absorbed through the skin during normal use or exposure to the compound.

Riihimäki and Pfäffli (1978) concluded that PERC concentrations found in ambient air were not likely to result in much PERC being absorbed through the skin. In their experiment, three individuals, wearing full facepiece respirators to prevent pulmonary absorption and dressed in thin cotton pajamas and socks, were exposed to 600 ppm (4,069 mg/m^3) PERC for 3.5 hours. During each midhour, for a period of 10 minutes, they exercised on an ergometer. Tidal and alveolar air (mixed) were collected in polyester-lined polyethylene bags. Concentrations of PERC in blood and in exhaled air were determined up to 20 and 50 hours, respectively. The amount absorbed (assuming 98 percent is exhaled) was calculated at 7 ppm (47.6 mg/m^3).

TABLE 5-1. ESTIMATED UPTAKE OF SIX INDIVIDUALS EXPOSED TO TETRACHLOROETHYLENE WHILE AT REST AND AFTER REST/EXERCISE (MONSTER, 1979)

	Uptake in mg					
Subject	72 ppm at rest	144 ppm at rest	142 ppm rest and exercise	Body mass kg	Lean body mass kg	Minute vol at rest 1/min
A	370	670	1,060	70	62	7.6
B	490	940	1,500	82	71	11.6
C	530	1,000	1,400	82	71	10.0
D	500	1,210	1,510	86	74	11.3
E	390	880	1,320	67	61	12.3
F	450	970	1,120	77	61	8.8

5.1.2. Distribution

Tetrachloroethylene is believed to be stored in body tissues having a high lipid content (Stewart, 1969). This storage site probably accounts for the prolonged retention of PERC. Such storage is suggested by the blood/air and fat/blood partition coefficients of 16 and 90, respectively (Monster, 1979). However, the time needed to saturate adipose tissue to 50 percent of its equilibrium concentration is high, about 25 hours.

In an abstract, Hake et al. (1976) reported that a small portion of PERC accumulated in the body. Males and females were exposed for 1.3, 5.5, and 7.5 hours per day to 25, 50, 100, and 150 ppm (170, 339, 678, and 1,017 mg/m^3).

Because of retention of PERC by adipose tissue, a long period (about two weeks) is necessary to eliminate PERC from the body completely (Monster et al., 1979; Fernandez et al., 1976) Stewart et al. (1970) reported results indicating that an accumulation will result during repeated exposures.

Guberan and Fernandez (1974), using a mathematical model to calculate uptake and distribution of PERC in the body, predicted that fatty tissues would show the slowest rate of PERC depletion because of the high solubility of PERC in fatty tissues. Serial breath concentration decay data obtained from 25 volunteers exposed to between 50 and 150 ppm (339 and 1,017 mg/m^3) for up to 8 hours were used in developing the model. As shown in Figure 5-1, theoretical curves of concentration in alveolar air (C_{alv}) divided by the concentration in inspired air (C_{ins}) versus exposure time for various post-exposure times can be used to estimate unknown concentrations to which an individual may be exposed.

Savolainen et al. (1977) found that exposure of two strains of rats to 200 ppm (13,560 mg/m^3) PERC for 6 hours daily, for 4 days resulted in retention of PERC in perirenal fat, brain, and liver. Statistical analyses were not performed.

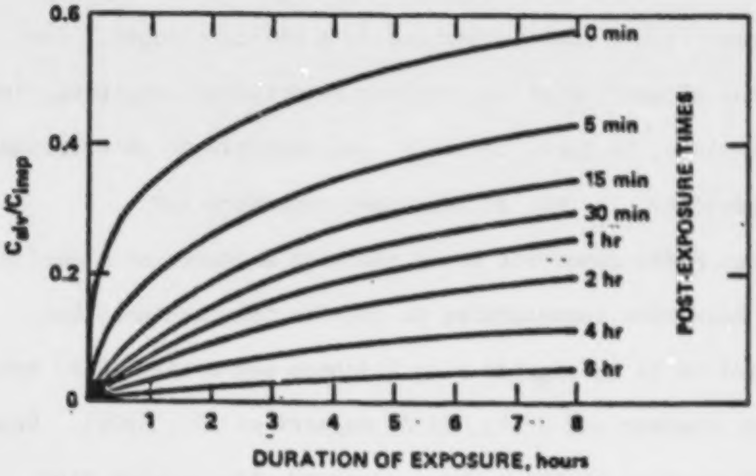


Figure 5-1. Predicted post-exposure alveloar air concentrations of PERC at various times against duration of exposure (Guberan and Fernandez, 1974).

When behavioral patterns were observed subsequent to the last exposure, ambulation frequency of exposed mice increased ($P < 0.05$) compared to controls. Rearing frequency, defecation and urination frequency, and preening frequency were not affected by exposure.

5.1.3 Metabolism (Animal Studies)

The hepatotoxic, carcinogenic, and mutagenic potentials of a number of chlorinated ethylene compounds (DHEW, 1977a; DHEW, 1977b; Viola et al., 1971; Maltoni and Lefemine, 1974; Creech and Johnson, 1974; Waxweiler et al., 1976; DHEW, 1977c) have generated considerable interest in the metabolic pathways of these compounds. Certain relatively inert chemicals are activated by biotransformation to carcinogenic intermediate metabolites which induce the carcinogenic lesion. Examining metabolic pathways is especially meaningful if it appears likely that a compound is a pro-carcinogen. The relationship of the metabolism of the various chlorinated ethylenes, including tetrachloroethylene, to their toxicity, and possibly to an assessment of their carcinogenicity, is thus an important consideration.

The cytochrome P-450 dependent mixed function oxidases of mammalian liver microsomes have been demonstrated to oxidize the carbon-carbon double bond in olefins to an epoxide ring (Liebman and Ortiz, 1968; Watabe and Maynert, 1968; Liebman and Ortiz, 1970; Maynert et al., 1970). Depending upon the configuration of the oxirane compound, the epoxide ring tends to be chemically quite unstable. This activated intermediate metabolite may thus interact covalently with a variety of groups in compounds of biological concern. When these compounds are nucleic acids and proteins that are essential to cellular function, the reaction may result in alteration of cellular metabolism, and cellular necrosis, or in carcinogenic or mutagenic lesions (Jerina and Daly, 1974).

The formation of an epoxide intermediate for a chloroethylene compound was originally postulated by Powell in 1945. Later, Yllner (1961) and Daniel (1963) speculated that PERC might be oxidized to an epoxide as an intermediate metabolite during its biotransformation. Recent interest in this hypothesis has resulted from findings that vinyl chloride is carcinogenic in man and animals (Viola et al., 1971; Creech and Johnson, 1974; Maltoni and Lefimine, 1974; Lee and Harry, 1974), and the observation that this in turn is likely due to the formation of an epoxide intermediate, chloroethylene oxide. This mechanism was proposed by van Duuren in 1975. A similar metabolic pathway and the production of epoxide intermediates for structural homologs of vinyl chloride has also been proposed by van Duuren (1975, 1977) and by Corbett (1975). The mechanism has gained support from several studies: (1) findings of covalent binding of ^{14}C-labeled vinyl chloride and trichloroethylene to tissue macromolecules, (2) catalyzation by rat liver microsomal preparations (Kappus et al. 1975; van Duuren and Banergee, 1976; Allemand et al., 1978), (3) by the formation of an alkylating metabolite, having an absorption spectrum identical with that of chloroethylene oxide, when vinyl chloride is incubated with mouse liver microsomal preparation (Barbin et al., 1975). Proof of the existence of any chloroethy lene epoxide in vivo has proven to be very difficult. Tetrachloroethylene epoxide, as well as other chloroethylene epoxides have been synthesized in vitro (Kline et al., 1978; Kline and van Duuren, 1977; and Derkosch, 1976). There epoxides are unstable (have short half-lives) and are highly reactive.

Yllner (1961) studied the metabolism of ^{14}C-labeled PERC in mice exposed for 2 hours by inhalation to doses of 1.3 mg/g. Seventy percent of the absorbed radioactivity was expired in air, 20 percent was excreted in the urine, and less than 0.5 percent was eliminated in the feces. Of the total amount of radioactivity excreted in the urine 52 percent was identified as trichloroacetic acid, 11 percent as oxalic acid, and a trace was dichloroacetic acid. No radiolabeled monochloroacetic acid, formic acid, or trichloroethanol was detected. Of the remaining radioactivity in the urine 18 percent was not extractable with ether, even after hydrolysis.

Daniel (1963) fed ^{14}C-labeled PERC to rats and found that excretion was largely of unchanged compound through the lungs (half-time of expiration was 8 hours). Only 2 percent of the radioactivity was excreted in the urine, and equimolar proportions of trichloroacetic acid and inorganic chloride were the only metabolites detected.

Other investigators (Ogata et al., 1971; Ikeda and Oktsuji, 1972; Ikeda, 1977; Moslen et al., 1977; Dmitrieva, 1967; Tada and Nakaaki, 1970; Boillat, 1970; Barchet et al., 1972) have reported that TCA is a urinary metabolite of PERC in experimental animals and humans.

The most likely pathway for such product formation would be via epoxidation of the double bond. The resulting chloro-oxirane compound is known to be unstable and rearranges spontaneously. However, the stability of symmetric oxiranes such as the one formed from PERC is greater than that of the asymmetric oxiranes such as those formed from vinyl chloride, vinylidene chloride, and trichloroethylene. Henschler and his colleagues (Bonse et al., 1975; Greim et al., 1975; Henschler et al., 1975; Bonse and Henschler, 1976) have studied the chemical reactivity, metabolism, and mutagenicity of the chlorinated ethylene series, including vinyl chloride, trichloroethylene, and tetrachloroethylene. These investigators have reported a correlation between biological activity and chemical structure:

those chlorinated ethylenes that are symmetrical such as cis-and trans-1,2-dichloroethylene and tetrachloroethylene are relatively stable and not mutagenic. In contrast, the asymmetrical ethylenes, vinyl chloride. vinylidene chloride, and trichloroethylene, are unstable and mutagenic. Although they recognized that oxiranes (epoxides) may be formed by all six of the chlorinated ethylenes, they concluded that the asymmetrical oxiranes are far less stable than the symmetrical ones, and therefore are more highly electrophilic, and may react directly with nucleophilic constituents of cells more readily, thereby exerting mutagenic or carcinogenic effects. The results of the mutagenic tests conducted by these investigators correlate with this structure-activity relationship.

Evidence for the involvement of the microsomal mixed-function oxidase system in the metabolism of PERC was shown by Moslen et al. (1977). Rats pretreated with phenobarbital or Arochlor-1254 (polychlorinated biphenyls)--inducers of the hepatic mixed function oxidase system--showed a significant increase in total trichlorinated urinary metabolites and trichloroacetic acid excretion following a single oral administration of 0.75 ml/kg PERC. Hepatotoxicity of PERC was enhanced by Arochlor-1254 pretreatment as evidenced by doubling of SGOT levels, and by the appearance of focal areas of vacuolar degeneration and necrosis of the liver. However, Cornish et al. (1973) did not observe a potentiation of tetrachloroethylene toxicity following intraperitoneal injection of 0.3 to 2.0 ml/kg PERC to rats pretreated with phenobarbital. [The LD50 for the mouse is 2.9 ml/kg (Klaasen and Plaa, 1966]. However, elevation of SGOT was noted at all dose levels in this study.

Recent *in vitro* studies concerning the extent of metabolism of PERC by Costa and Ivanetich (1980) provide further evidence of the central role of hepatic microsomal cytochrome P-450 in the metabolism of PERC. Two distinct forms of P-450, one induced in vivo in rats by phenobarbital and the other by pregnenolone-16α-carbonitrile were shown to be active in the in vitro binding and metabolism of PERC. P-448, induced by β-napthoflavone, was not active in the in vitro system.

Spectral binding of PERC to P-450 in microsomes was measured by the difference in absorbance between 386 nm and 418 nm. Metabolism was estimated in vitro by the maximal rate of production (V_{max}) of trichloroacetic acid (TCA) per minute per nmole P-450. The spectral binding constant (K_s) associated with P-450 from uninduced rats was 0.4 mM. Phenobarbital-induced P-450 had no effect on K_s but P-450 from pregnenolone-16α-carbonitrile-induced rats increased K_s.

V_{max} was significantly ($P<0.01$) increased above controls (uninduced rats) whether the microsomal preparation was derived from either of the inducers. Phenobarbital induction resulted in a lowering of the Michaelis-Menton (K_m) constant, indicating an increased affinity for the associated enzymes. The K_m was increased when the microsomes were derived from pregnenolone-16α-carbonitrile induction. β-napthoflavone, a P-448 inducer had no effect on any of these parameters.

The rate of carbon monoxide-inhibitable NADPH oxidation by PERC was elevated significantly ($P<0.01$) above noninduced controls by phenobarbital-induced microsomes. Induction by pregnenolone-16α-carbonitrile was without effect in this system.

Metyrapone, a specific inhibitor of P-450, reduced spectral binding, NADPH oxidation, and metabolism by PERC, 80, 65, and 75 percent, respectively. SKF-525A reduced spectral binding and metabolism, 19 and 33 percent, respectively.

The microsomal preparation used in the system was derived from phenobarbital-treated rats.

The major metabolite in the in vitro system was observed to be unbound TCA. Trichloroethanol was not found in appreciable amounts.

Levels of P-450, as well as cytochrome b_5, heme, NADPH-cytochrome reductase and glucose-6-phosphatase were not reported to be altered, whether the inducer was phenobarbital or pregnenolone-16α-carbonitrile.

The extent of metabolism of PERC and its binding to hepatic macromolecules, in both mice (B6C3F1) and rats (Sprague-Dawley) was investigated by Schumann et al. (1980). Animals were exposed for 6 hours via inhalation to 10 and 600 ppm (67.8 and 4,068 mg/m^3) ^{14}C-labelled PERC with a specific activity of 2.6 mCi/mmole. Purity was determined to be > 98 percent. In an acute oral dosing experiment, rats and mice were administered 500 mg ^{14}C-labelled PERC/kg body weight. Following inhalation of 10 ppm (67.8 mg/m^3) ^{14}C-labelled PERC by mice, it was observed that urinary metabolites accounted for 62.5 percent of total radioactivity recovered while PERC unchanged in expired air accounted for only 12.0 ± 1.3 percent. The reverse situation was observed after a single oral dose of 500 mg/kg: 82.6 percent of total recovered radioactivity was in the form of unchanged PERC in expired air. Metabolites accounted for 10.3 percent. When compared to the extent of metabolism in rats (Pegg et al., 1979), it was calculated that the mouse metabolized 8.5 and 1.6 times more PERC/kg than rats at 10 ppm (67.8 mg/m^3) and 500 mg/kg, respectively.

Following exposure of rats and mice to 10 and 600 ppm (67.8 and 4,068 mg/m^3), no radioactivity was observed to be bound to purified hepatic DNA. The detection limit was 14.5 alkylations/10^6 nucleotides at the 600 ppm (4,068 mg/m^3) level. Lack of binding to DNA also was observed following a single oral dose of 500 mg/kg. However, at times of peak binding to hepatic macromolecules, 4.7, 5.8, and 4.4 fold more radioactivity was irreversibly bound in the mouse than in the rat following 10 or 600 ppm (67.8 or 4,068 mg/m^3), or 500 mg/kg, respectively. The extent of hepatic macromolecular bindings was determined subsequent to homogenization of the liver. It was noted by the authors that the 60-fold increase in exposure level resulted in a 10-fold increase in the extent of binding in both rats and mice. This was suggestive that metabolism of PERC is a saturable process. Binding was determined at intervals up to 72 hours postexposure. The lack of binding to DNA was suggested by the authors as evidence indicating the PERC lacks genotoxic potential. It should be noted that an absence of binding to DNA dose not preclude such an event that occurs below the detection limit of alkylation. Effects of treatment on body weight and liver are reported in Chapter 6. A briefer discussion of the results of Schumann and coworkers was presented by Watanabe et al. (1980).

In the oral and inhalation exposure of male Sprague-Dawley rats, Pegg et al. (1979) found that, by either route, PERC was eliminated in unchanged form, predominantly in expired air. In contradistinction to evidence pertaining to humans and other species, Pegg and coworkers found oxalic acid to be the major urinary metabolite. TCA was not detected.

The protocol was similar to that used by Schumann et al. (1980) in exposures of mice and rats. Rats were exposed via inhalation (6 hours) to 10 and 600 ppm (67.8 and 4,068 mg/m^3) ^{14}C-labelled PERC. In the gavage experiment 1 or 500 mg ^{14}C-labelled PERC/kg body weight was administered as a single dose.

After oral administration (500 mg/kg) or inhalation (600 ppm; 4,068 mg/m^3), 89 percent of the radioactivity was recovered in expired air as PERC; 1 to 2 percent remained in the carcass. The difference was accounted for by $^{14}CO_2$ and urinary and fecal metabolites. Pulmonary elimination was observed to be monophasic with a half-life of about 7 hours; it was independent of dose or route of administration. Radioactivity remaining in the carcass 72 hours after exposure by either route was primarily distributed in liver, kidney, and fat tissue. After oral administration of 1 mg/kg, only 72 percent of the radioactivity was recovered in expired air as PERC. Recovery of $^{14}CO_2$ and nonvolatile metabolites increased. It was suggested by the authors that, in rats, metabolism of PERC is a saturable process.

In blood, PERC levels peaked 1 hour after oral administration. Disappearance followed apparent first order kinetics for up to 36 hours after exposure with a half-life of 6 hours, and an elimination constant of 0.12 hr.$^{-1}$. After termination of exposure to 600 ppm (4,068 mg/m^3), PERC levels in blood declined similarly with a half-life of 7 hours and an elimination constant of 0.10 hr.$^{-1}$.

Whole liver radioactivity and that associated irreversibly with tissue macromolecules were assayed 0, 6, 24, and 72 hours after termination of exposure to 10 or 600 ppm (67.8 or 4,068 mg/m^3) and 72 hours after oral administration. Whole liver radioactivity in livers from inhalation-exposed animals decreased exponentially during the 72 hours collection period as a biphasic process. The ratio of bound to metabolized radioactivity 72 hours after oral or inhalation exposure was not significantly different between the high and the low dose.

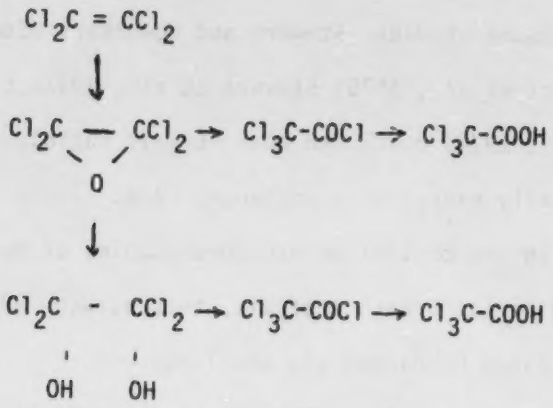
Nonprotein liver sulfhydryl levels were not found to be depleted and suggested to the authors that glutathione was not involved in metabolism. The low rate of turnover of nonextractable radioactivity in liver macromolecules also suggested that accumulation of bound PERC metabolites could potentially occur upon repeated exposure.

Vainio et al. (1976) looked at the effects of PERC on liver metabolizing enzymes in vivo--in the rat. Oral administration of 2.6 mmol/kg PERC was associated with a statistically significant lowering of levels of 3,4-benzpyrene hydroxylation and p-nitroanisole-o-methylation.

Plevova et al. (1975) showed that 6 hours of inhalation of 12 mg/liter tetrachloroethylene 20 hours prior to 2 ml/kg i.p. pentobarbital would lengthen pentobarbital sleeping time by 30 percent in Wistar rats. This effect was possibly mediated through hepatic drug metabolizing enyzme activity. Also, changes in spontaneous motor activity induced by intraperitoneal injection of pentobarbital, diazepam, amphetamine, and partly by chlorpromazine were enhanced by previous inhalation of PERC. This was probably due to an effect on metabolism rates.

Although, as mentioned previously, trichloroacetic acid has been observed by several investigators to be a urinary metabolite of tetrachloroethylene, the excretion of total trichloro compounds, as measured by the Fujiwara colorimetric reaction after oxidation, exceeded that of trichloroacetic acid--in some cases this was assumed to be trichloroethanol (Muenzer and Heder, 1972; Ikeda et al., 1972). In other studies that portion which was not trichloroacetic acid could not be demonstrated to be trichloroethanol (Hake and Stewart, 1977). In one report ethylene glycol was claimed to be a prominent metabolite in the rat (Moslen et al., 1977).

Leibman and Ortiz (1975, 1977) proposed a scheme for possible pathways of PERC metabolism. The formation of tetrachloroethylene epoxide by the hepatic mixed function oxidase system may be followed by hydration of the epoxide to tetrachloroethylene glycol. Due to the symmetric arrangement of the epoxide and the glycol intermediates, rearrangement of both would yield trichloroacetyl chloride, which hydrolyzes rapidly to trichloroacetic acid and, to a much lesser extent, TCE in the urine.



$$\mathrm{Cl_2C=CCl_2}$$
$$\downarrow$$
$$\underset{\mathrm{O}}{\mathrm{Cl_2C-CCl_2}} \rightarrow \mathrm{Cl_3C\text{-}COCl} \rightarrow \mathrm{Cl_3C\text{-}COOH}$$
$$\downarrow$$
$$\underset{\mathrm{OH}}{\mathrm{Cl_2C}} - \underset{\mathrm{OH}}{\mathrm{CCl_2}} \rightarrow \mathrm{Cl_3C\text{-}COCl} \rightarrow \mathrm{Cl_3C\text{-}COOH}$$

Incubation of PERC and rat liver supernatant with a nicotinamide adenine dinucleotide phosphate, reduced, (NADPH) generating system confirmed the production of trichloroacetic acid. Nicotinamide adenine dinucleotide, reduced (NADH), did not promote the formation of trichloroacetic acid. Expoxide hydrase inhibition, produced by the addition of cyclohexane to the incubation mixture, did not have any effect upon trichloroacetic acid formation. Leibman and Ortiz concluded that, if the epoxide-diol pathway is operative, trichloroethylene oxide is not a substrate for hydration by epoxide hydrase, or that the epoxide and glycol rearrange to trichloroacetyl chloride at similar rates.

5.1.4 Excretion and Elimination

Tetrachloroethylene is removed from the body in two principal ways: elimination as an unchanged compound in exhaled air and through elimination of its metabolites.

During exhalation, the concentration of PERC in expired air is a function of a number of factors: (1) duration of exposure and the concentration in inhaled air, (2) rate of respiration, (3) time elapsed following exposure, and (4) total body lipid and other tissue repositories. The principal approach used to measure the amount and kinetics of elimination via the lungs is serial breath analysis of alveolar air.

From controlled exposure studies, Stewart and coworkers (Stewart, 1969; Hake et al., 1976; Stewart et al., 1970; Stewart et al., 1961a,b; Stewart et al., 1977; Stewart et al., 1974) concluded that PERC is rapidly excreted from the lungs and is principally excreted in unchanged form. These findings have recently been confirmed in the controlled exposure studies of Monster et al. (1979), who found, using serial breath analysis, that between 80 and 100 percent of PERC is eliminated unchanged via the lungs.

The principal urinary metabolite of PERC is trichloroacetic acid (TCA), although trichloroethanol (TCE) has been reported to be a secondary metabolite. Other minor metabolites reported include oxalic acid, dichloroacetic acid, and ethylene glycol.

5.1.4.1 Controlled Studies--The concentration in alveolar air in the most immediate post-exposure period (up to 2 hours) is a reflection of the PERC concentration to which the individual was most recently exposed (Stewart et al., 1970; Stewart 1961b). The breath decay curves shown in Figure 5-2 were obtained from five males experimentally exposed to an average PERC concentration of 101 ppm (685 mg/m^3) for 7 hours per day on 5 consecutive days. The curves show that a high percentage of absorbed PERC was excreted during each two-week period following exposure. A single 7-hour exposure of 15 volunteers to an average PERC concentration of 101 ppm (685 mg/m^3) resulted in a similar alveolar desaturation curve (Stewart et al., 1970). The range of concentrations from which the average was obtained was 62 to 137 ppm (420 to 929 mg/m^3). The increase of inital alveolar air concentrating after repeated exposure (Figures 5-2 and 5-3) was suggested to be a result of the accumulation of PERC in the body tissues. The "hump" in the curve (Figure 5-3) is unexplained but was not considered by the authors to be artifactual. Breath samples, collected in glass pipettes and Saran® bags, were analyzed by infrared spectroscopy.

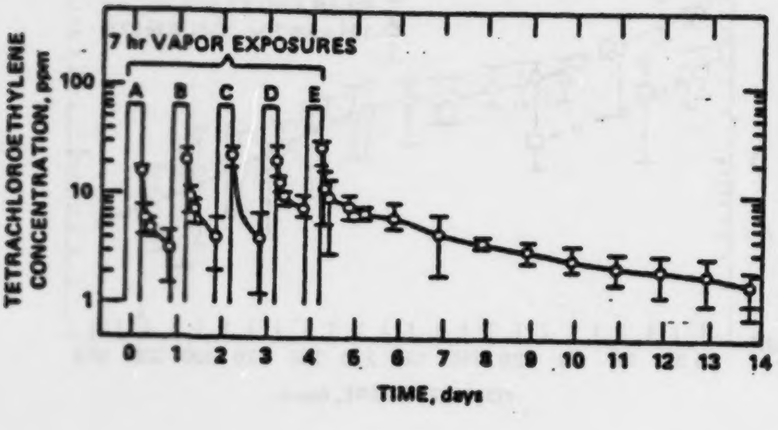


Figure 5-2. Mean and range of breath concentrations of tetrachloroethylene after exposure of individuals to a single or repeated exposures (Stewart et al., 1970.

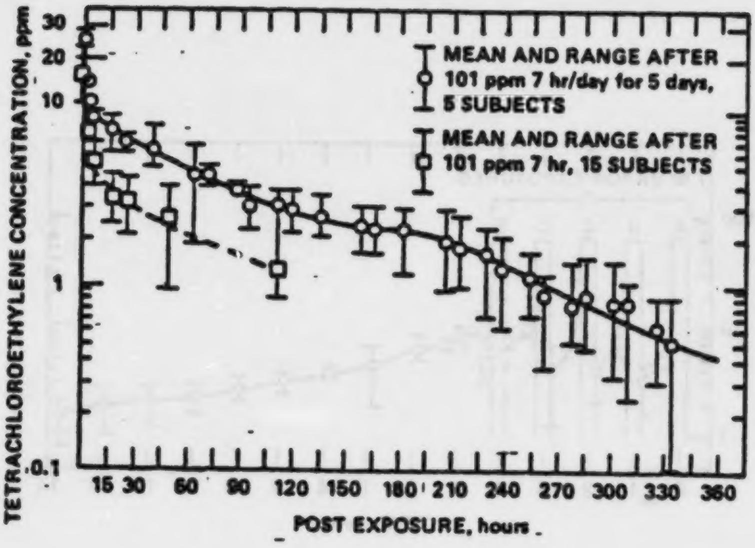


Figure 5-3. Mean and range of breath concentrations of five individuals during postexposure after five separate exposures to 96, 109, 104, 98, and 99 ppm (Stewart et al., 1970.

After an exposure (Stewart et al., 1961a) of six volunteers to approximately 100 and 200 (678 and 1,356 mg/m^3) PERC, analyses of the breath decay curves indicated that (1) exposures of similar duration yielded decay curves with similar elimination rate constants, (2) the average concentration in the expired air was reflective of the vapor concentration for exposures of similar duration, and (3) the length of time PERC can be measured in expired air was proportional to both the vapor concentration and the duration of exposure.

The concentration of PERC in the blood of those individuals exposed to 194 ppm (1,316 mg/m^3) for 83 and 187 minutes approached a plateau near the end of the third hour of exposure. After exposure PERC was rapidly cleared from the blood and was undetectable 30 minutes later.

Evidence for a high rate of pulmonary absorption of PERC was reported by Bolanowska and Golacka (1972). Five individuals were exposed to 51 ppm (390 mg/m^3) PERC for 6 hours; only 25 percent of the absorbed dose was reported to have been eliminated via the lungs. However, it appears that the amount excreted had been greatly underestimated by the authors (Davidson, 1978).

Monster et al. (1979), in agreement with the general findings of Stewart and co-workers (Stewart, 1969; Hake et al., 1976; Stewart et al., 1970; Stewart et al., 1961a,b; Stewart et al. 1977; Stewart et al., 1974) found that 80 to 100 percent of the PERC absorbed was excreted unchanged; metabolism to urinary trichloroacetic acid (TCA) accounted for less than 2 percent. Physical exercise resulted in increased uptake and an increase of PERC in blood levels; similar observations were made by Stewart et al. (1974).

In the study by Monster et al. (1979) discussed previously in section 5.1.1.1, the concentration of PERC in exhaled air decreased upon exercise of the individuals being exposed. Recovery in exhaled air was 78 percent (exercise) as compared to 92 percent when the individuals were at rest. Exercise had no effect on the half-life of PERC elimination or on the rate constant of elimination. Minute volume and lung clearance were three-fold higher than the values obtained when the individuals were at rest. While exercise decreased the amount of PERC in exhaled air, uptake increased about 40 percent (Figure 5-1).

The concentrations of PERC in blood and in exhaled air during the post-exposure period are shown in Figure 5-4. Contrary to the finding of Stewart et al. (1961a) that blood concentrations of PERC were undetectable 30 minutes after exposure, Monster et al. (1979) found that the decrease of PERC in the blood paralleled the decay in expired air. The slopes of the curves in Figure 5-3 suggest that the half-lives of PERC in exhaled air and blood for three body compartments are (1) tissues with high blood flow, (2) lean tissue, and (3) adipose tissue. The concentration of TCA (from metabolism) in the blood increased for 20 hours post-exposure before declining. Monster (1979) suggested that the increase in TCA concentration is smaller and the maximum reached earlier in contrast to exposures to trichloroethylene or methyl chloroform. The biological half-life of TCA in blood is the same for all solvents (about 80 to 100 hours). Upon repeated exposure to PERC, TCA would increase (Monster et al., 1979).

The time course of the PERC concentrations in blood and in expired air indicates that a long (> 275 hours) period is necessary to eliminate PERC from the body completely (Fernandez et al., 1976; Monster et al. 1979).

Fernandez et al. (1976) found that 2 weeks were necessary to eliminate PERC completely from the body after exposure to 100 ppm (678 mg/m^3) for 8 hours. These findings are in agreement with those of Monster et al. (1979). In these chamber studies, 24 volunteers were exposed for 1 to 8 hours to vapor containing 100, 150, and 200 ppm (678, 1,017, and 1,356 mg/m^3) PERC. When exposure time increased, the PERC concentration in alveolar air increased. However, there was no direct proportionality between the period of exposure and the PERC concentration in the alveolar air samples. An accumulation of PERC in the body will result during repeated exposures was suggested by Stewart et al., (1970) and Monster et al., (1979). After exposure, the blood concentration of PERC paralleled exhaled air concentrations (Figure 5-4) and was 23 times higher than PERC in expired air.

Monster (1979) determined that the values for partition coefficients and lung clearance measurements between blood/vapor after exposure of 4 to 6 individuals to 70 to 140 ppm (475 and 950 mg/m^3) PERC for 4 hours indicated that (1) alveolar air concentration of PERC in the first few hours after exposure will be proportional to exposure concentration and to concentration in blood and other rapidly exchangeable tissues, and (2) during that later phase of elimination the alveolar air concentration will be proportional to the concentration in adipose tissue. As previously stated, the partition coefficient (37°C) for PERC between venous blood/alveolar air of 16 and the partition coefficient between fat/blood of 90 suggests that apidose tissue is a primary storage site. It was estimated that 25 hours would be necessary for PERC to saturate adipose tissue to 50 percent of its equilibrium concentration with plasma.

Metabolic considerations investigated in this study are discussed in Sections 5.1.3 and 5.1.4.

Evidence that blood levels of PERC may be useful in determining individual uptake was obtained in a single exposure to 70 and 140 ppm (475 and 950 mg/m^3) for 4 hours (Monster and Houtkooper, 1979). Concentrations of PERC in blood, urine, and exhaled air were determined at 2 and 20 hours after exposure. While a high degree of correlation was obtained between

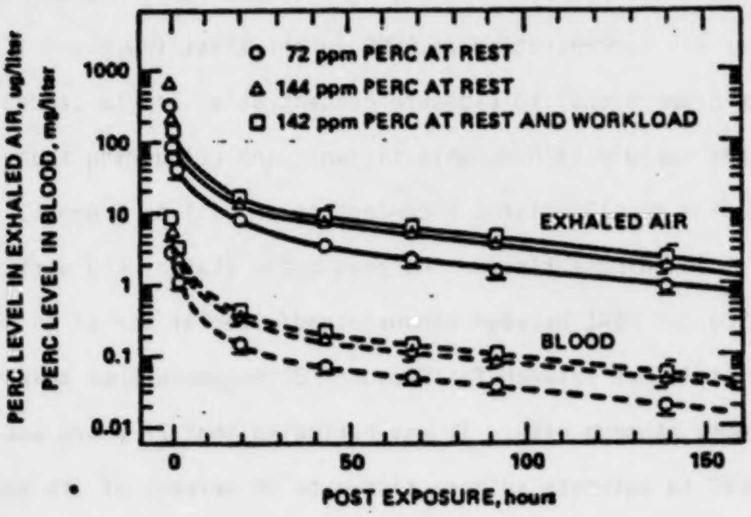


Figure 5-4. Tetrachloroethylene in blood and exhaled air following exposure to PERC for 4 hours. Each point represents geometric mean ± standard deviation of six individuals. (Monster et al., 1979)

exhaled air concentration and blood concentration, linear and multiple linear regression analysis showed an inter-person coefficient of variation of 20 to 25 percent for blood measurements at 2 and 20 hours and in exhaled air at 2 hours.

Verbeck and Scheffers (1980) suggest that measurements of PERC in expired air are useful in monitoring exposure in the general population as well as in populations of occupationally exposed people. Tetrachloroethylene was measured in the expired air of residents living near 12 dry cleaning shops. Residents were classified into two groups, corresponding to the distance they lived from the shops. In all cases, the residents living nearest the shop, the house next to the shop, had higher levels of PERC in expired air than residents who lived one house farther away from the shop.

In the study by Stewart and Dodd (1964), elimination of PERC through the skin following percutaneous absorption was shown to be minor. Each of five individuals immersed one thumb in a beaker of PERC located in a ventilated hood. At intervals of 10 minutes, the concentration of PERC in exhaled air was measured. Before and periodically during each skin exposure, samples of breathing zone air were analyzed to preclude solvent vapor contamination. The mean peak breath concentration after a 40-minute immersion was 0.31 ppm (2.1 mg/m^3); 2 hours after exposure the mean breath concentration was 0.23 ppm (1.6 mg/m^3). Five hours after exposure, PERC was still detectable (0.16 to 0.26 ppm; 1.1 to 1.8 mg/m^3).

The elimination of PERC through the skin was found by Bolanowska and Golacka (1972) to be approximately 0.02 percent per hour of the dose inhaled. One hand of a vapor-exposed individual was placed in an aluminum foil bag covered with polyethylene and selaed. After 1 hour the bag was removed and the PERC concentration in the air it contained was measured. In calculating the elimination through the skin, the authors assumed that the surface of one upper extremity is about 9 percent of the surface of the entire.

As previously mentioned, in both controlled and occupational exposures of humans to PERC, the principal urinary excretion product is trichloroacetic acid (TCA). Trichloroethanol (TCE) has been reported as a metabolite. It was indirectly measured by chromate oxidation of urine to TCA.

Hake and Stewart (1977) found only traces of TCA in 24-hour urine specimens from individuals exposed to 150 ppm (1,017 mg/m^3) PERC and below. No TCE was detected.

Ogata et al. (1971) found TCA in the urine of four individuals exposed to 87 ppm (590 mg/m^3) PERC for 3 hours at a level of 1.8 percent of the total PERC dose. Trichloroethanol could not be detected, but the urine did contain 1 percent of an unidentified chlorine-containing compound. Urine was collected for 67 hours into the post-exposure period.

In the studies of Monster and co-workers discussed previously (Monster et al., 1979; Monster and Houtkooper, 1979), urinary TCA was found to represent less than 1 percent of the absorbed dose of PERC. In blood, TCA continued to increase until 20 hours post-exposure. From about 60 hours after exposure, the concentration decreased exponentially. A base level of 0.6 mg TCA per day was found in the urine of subjects prior to exposure. Results of blood and urine concentrations are shown in Figures 5-5 and 5-6. The ratio of TCA_{urine} and TCA_{blood} was three-fold higher in the period 0 to 22 hours after start of the exposure. The relatively high concentration in urine possibly was due to an unknown compound measured by the non-specific Fujiwara reaction; TCA in blood was measured by gas chromatography. The unknown compound was not PERC or TCE.

Exposure combined with exercise resulted in 20 percent higher levels of TCA excreted, while uptake of PERC increased 40 percent. The TCA concentration at 20 hours after exposure was 1.6 times the concentration at the end

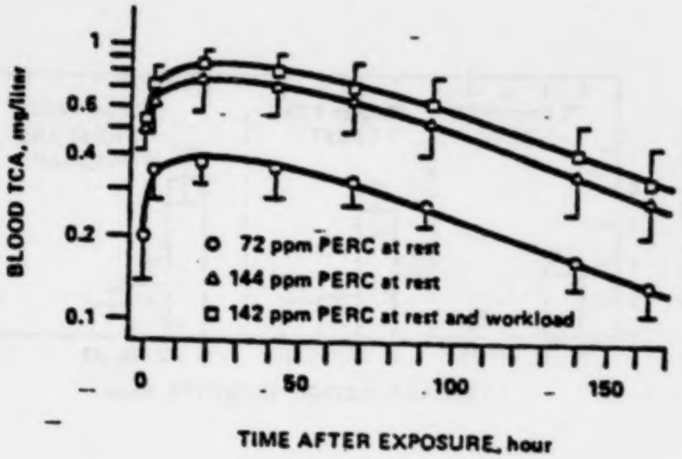


Figure 5-5. Trichloroacetic acid (TCA) in blood following exposure to PERC for 4 hours. Each point represents the geometric mean ± the standard deviation of six subjects (Monster et al., 1979).

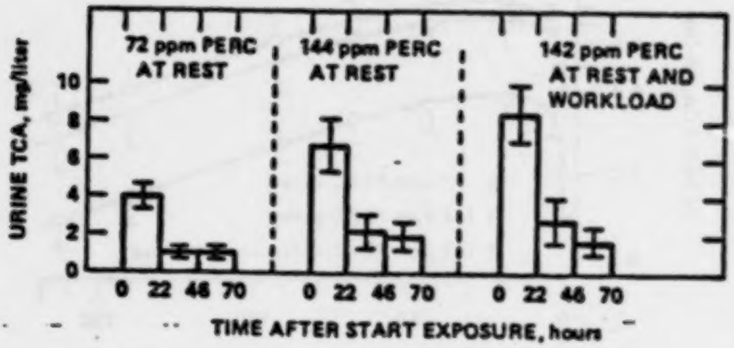


Figure 5-6. Urinary Excretion of trichloroacetic acid (TCA) following exposure to PERC for 4 hours. Each point represents the mean ± the standard deviation of six subjects (Monster et al., 1979).

of exposure. Inferences drawn from these results regarding metabolism of PERC are discussed in Section 5.1.3. It was concluded that TCA is not a reliable indicator of exposure to PERC (Monster and Houtkooper, 1979).

5.1.4.2 Occupational Studies--In a study involving six dry cleaning plant workers exposed to PERC, an increase in urinary TCA was observed over the 50-hour sampling period (NIOSH, 1974). A control group not exposed to significant quantities, also evidenced a similar increase. The average length of exposure for these individuals was 17 months. The worker evidencing the highest level of TCA in the urine had been exposed to an 8-hour time-weighted average of 168 to 171 ppm (1,139 to 1,160 mg/m^3) PERC.

Trichloracetic acid and TCE were found in the urine of 40 workers exposed to PERC concentrations ranging from 58 to 134 ppm (393 to 909 mg/m^3) (Medek and Kovarik, 1973). The maximum levels observed were 41 mg TCA and 116 mg TCE per liter of urine. Seventy-two percent of these workers reported subjective complaints.

Muenzer and Heder (1972) reported that urinary TCA was found in 124 of 200 dry cleaning plant employees. Seventy-one individuals had more than 10 mg per liter. Liver function tests for exposed and unexposed (control) groups were comparable. The general room air in the work places contained between 200 to 300 ppm (1,357 to 2,035 mg/m^3) PERC. An association between workroom air concentrations and TCA levels was not made.

Ikeda et al. (1972) reported evidence that TCA and TCE concentrations in the urine increased in proportion to environmental concentrations of PERC up to 50 ppm (339 mg/m^3). In this study, urine samples were collected from 34 male industrial workers who had been exposed to PERC vapors for 8 hours per day, 6 days per week. Concentrations of PERC in the work place ranged from 10 to 400 ppm (68 to 2,713 mg/m^3). The plateau observed in the urinary excretion curve for TCA suggested to the investigators that the capacity of humans to metabolize PERC is limited. The maximum level of TCA observed was approximately 50 mg per liter of urine. For TCE, the maximum concentration reported was approximately 25 mg per liter. Trichloroethanol was measured indirectly by oxidation of urine with chromic oxide.

In another study, Ikeda and Ohtsuji (1972) reported a wide variation in the TCA and TCE levels in urine from occupationally exposed workers. One group of four had been exposed to a concentration range of 20 to 70 ppm (136 to 475 mg/m^3), while 66 workers in another group had been exposed to between 200 and 400 ppm (1,357 and 2,713 mg/m^3). The urine from the smaller group contained between 4 and 35 mg TCA and 4 to 20 mg TCE per liter of urine. In the larger group, TCA levels were 32 to 97 mg per liter and TCE levels ranged from 21 to 100 mg per liter.

High levels of TCA (>60 mg/liter of urine) also were reported by Weiss (1969) and by Haag (1958) in studies of individuals exposed occupationally.

The findings, if confirmed, that TCE may be a metabolite of PERC are of toxicological importance since this presumed metabolite has been reported to be neuro- and cardiotoxic (Mikiskova and Mikiska, 1966). Further research in this area is suggested.

5.1.4.3 Population Studies--Preliminary results reported by Ziglio (1980) suggest that plasma TCA can be a reliable indicator of the extent of chronic exposure to PERC. Ziglio chose 24 individuals in Milan, a city in which both trichloroethylene and PERC were present in tap water at concentrations as high as 150 to 200 μg/l (Giovanardi, 1979). Subjects were divided into two groups: exposed (those who drank water with halocarbon levels $\geq$ 50 μg/l) and nonexposed (those who drank water with levels $\leq$ 1 μg/l). When exposure increased, plasma TCA levels increased. However, the TCA levels were suggested by Ziglio to be more indicative of the extent of exposure to trichloroethylene, since this halocarbon is metabolized to a much greater extent than is PERC.

5.1.5 Estimates of Biological Half-Life

Monster et al. (1979) determined from the concentration curves of PERC in blood and exhaled air after exposure (Figure 5-4) that PERC was eliminated from the body at three different rate constants with corresponding half-lives of 12 to 16, 30 to 40, and 55 hours, respectively, and suggesting three major body compartments for PERC. The half-life, derived from the data of Stewart et al. (1970) was calculated to be 65 hours.

Trichloroacetic acid in blood was reported by Monster et al. (1979) to have a predominant half-life (60 hours after exposure) of 75 to 80 hours.

Ikeda (1977) and Ikeda and Imamura (1973) reported that the mean biological half-life for PERC urinary metabolites is 144 hours. A possible sex difference, indicated from exposures of 9 males and 4 females, is yet to be confirmed.

The estimated biological half-life of PERC stored in adipose tissue is 71.5 hours (Guberan and Fernandez, 1974).

5.1.6 Interaction of PERC with Other Compounds

In a study designed to determine the effects of alcohol and diazepam (Valium) on 12 individuals exposed to 25 and 100 ppm (170 and 678 mg/m^3) PERC for 5.5 hours, Stewart and co-workers (1976) found altered blood levels of the halocarbon. Administration of alcohol to individuals during exposure to 25 ppm (170 mg/m^3) significantly increased blood levels of PERC ($p<0.01$). There was no effect during exposure at 100 ppm (678 mg/m^3). Diazepam and alcohol each raised both blood and breath levels of PERC during exposure at 25 ppm (170 mg/m^3). Results are shown in Table 5-2. It was concluded that neither diazepam nor alcohol exacerbated or enhanced the effects of PERC as measured by behavioral and neurological tests.

TABLE 5-2. ALCOHOL AND DIAZEPAM EFFECTS UPON TETRACHLOROETHYLENE BLOOD AND BREATH LEVELS, 5-1/2 HOUR EXPOSURES (Stewart et al., 1977)

PERC in Chamber, PPM	PPM PERC in blood			PPM PERC in breath					
	@ 2 hours into exposure			@ 2 hours into exposure			@ 30 minutes post exposure		
	PERC alone	PERC + alcohol[a]	PERC + diazepam[b]	PERC alone	PERC + alcohol[a]	PERC + diazepam[b]	PERC alone	PERC + alcohol[a]	PERC + diazepam
25	1.65 (35)	2.92** (15)	1.76 (23)	11.03 (35)	12.35* (15)	11.72 (23)	6.40 (35)	7.49** (14)	6.96* (22)
100	8.25 (63)	7.95 (29)	8.47 (41)	33.2 (68)	32.3 (28)	35.5 (44)	17.62 (64)	13.83** (29)	17.35 (42)

[a] Alcohol blood levels of 30 to 100 mg percent.

[b] Diazepam blood levels of 7 to 30 mcg percent.

*Significantly different from PERC alone at $p<.05$.

**Significantly different from PERC alone at $p<0.1$.

(n)Number of determinations.

5.1.7 Summary

Evidence from both human and animal exposure studies, as well as *in vitro* data, suggest that there are metabolic distinctions between humans and rodents. Inhalation is the predominant route of exposure for humans although contamination of potable water supplies indicates that oral ingestion represents an additional burden.

In all species tested, PERC is rapidly absorbed and distributed to major body compartments. Because of its high octanol/water and fat/blood partition coefficients, PERC can be expected to accumulate during repeated exposures in lipid-rich tissues. Up to two weeks or more may be required to eliminate PERC completely from the human body (Fernandez et al., 1976). Retention of PERC in lipid-rich tissues has been observed (Pegg et al., 1979) in rats. The estimated biological half-life of PERC in adipose tissue is about 70 hours. It would also be expected to accumulate in lungs, liver, kidney, spleen, and lean muscle.

PERC is postulated to be metabolized via oxidation by the cytochrome P-450 mixed function oxidase system. An epoxide intermediate, formed during metabolism, is believed to represent a highly active, unstable species capable of binding covalently to tissue macromolecules. *In vitro* experiments (Costa and Ivanetich, 1980) have shown that a cytochrome P-450 activation system from rats binds and metabolizes PERC; TCA was identified as the principal reaction product. The *in vivo* studies by Pegg et al. (1979) in rats and by Schumann et al. (1980) in mice have demonstrated irreversible binding of PERC and/or its metabolites to hepatic macromolecules; binding to DNA was not observed. It would be expected that unless the metabolic pathways and activated intermediates differ, PERC metabolites would be expected to bind to human hepatic macromolecules as well.

In humans, mice, and rats, the predominant urinary metabolite is trichloroacetic acid (TCA) in humans, TCA accounts for 2 percent or less than the absorbed dose. The estimated mean biological half-life for all urinary metabolites is 144 hours. Minor metabolites reported include trichloroethanol, oxalic acid, trichloroacetic acid, and ethylene glycol. TCA also is the predominant urinary metabolite in mice. Pegg et al. (1979) however, observed oxalic acid to be the principal urinary metabolite in rats. TCA was not detected upon incubation of a rat hepatic microsomal activation system with PERC. Costa and Ivanetich (1980) observed TCA to be the principal reaction product.

Elimination of PERC in expired air differs somewhat between humans, mice, and rats. Monster and coworkers (1979) have shown that more than 80 percent of PERC is recovered unchanged, in expired air. Exercise has the effect of increasing uptake in the body. Repeated exposures to levels of 72 ppm or greater during sedentary conditions was observed to result in more PERC being eliminated unchanged in expired air. At expected ambient air levels of exposure (<10 ppb), increased elimination upon repetitive exposure may not take place since the blood/air and fat/blood partition coefficients favor uptake, particularly at low exposure levels.

Elimination as the unchanged compound in expired air also is the predominant process in rats (Pegg, et al. 1979), upon inhalation or oral exposure. In mice, however, urinary metabolites represent the chief elimination process (Schumann et al., 1980). Upon oral exposure of mice, pulmonary elimination predominates (Schumann et al. 1980).

The dose level is a factor of particular importance when one considers the potential effects of PERC. There appears to be little evidence that a more hazardous metabolite or a distinctively different pharmacokinetic pattern will result from exposure to high dose levels. Monster et al. (1979) has shown that a two-fold increase in exposure level resulted in a doubling of uptake; a shift in the nature of the urinary metabolites was not observed.

Kraybill and Mehlman (1977) and Page (1977), in recent reviews of carcinogenicity testing methods, suggested that extrapolation from high dose levels may, in some cases, underestimate the actual effect that occurs at low dose levels. This might happen when exposure levels exceed the capacity of the body to absorb, or when an inactive chemical species is metabolized to an activated carcinogenic intermediate by a system of finite capacity. Sequential increases in exposure levels may not result in incremental increases in effect. Similar reasoning was applied by Schumann et al. (1980) to explain the reason why exposure of mice to 500 mg/kg is carcinogenic and the lack of a dose-response when 1,000 mg/kg is administered. It was suggested by these authors that the metabolism of PERC is saturable at some exposure level; at levels below saturation detoxification/repair processes have the fidelity to insure that low levels of exposure do not result in deleterious effects. However, it should be noted that the capabilities of the human and rodent defense mechanisms with regard to low-level exposures to PERC are unknown.

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6. TOXICOLOGY: EFFECTS RESULTING FROM ACUTE, SUBCHRONIC AND CHRONIC EXPOSURE SITUATIONS

6.1 HUMANS

The known effects of tetrachloroethylene (PERC) on humans have been established primarily from individuals accidentally or occupationally exposed to high (in some cases, unknown) concentrations of PERC. Exposure to PERC causes a wide variety of toxicological effects in humans. Effects upon the central nervous system (CNS) are generally the most noticeable following acute or occupational exposures. Effects upon the liver and kidney usually are observed after an elapsed period of time.

In order to relate health effects of PERC to exposure levels of PERC that one might reasonably expect in ambient exposure situations, it is the intent of this section to focus on those effects associated with the lowest levels of PERC. Both acute and chronic exposure situations and associated effects are delineated.

6.1.1 Effects on the Liver

6.1.1.1 Acute Exposure Situations--Mild hepatitis was diagnosed by Stewart (1969) in a worker occupationally exposed to high, unknown concentrations of PERC for less than 30 minutes. Infrared analysis of the patient's exhaled breath 1.5 hours after exposure showed 105 ppm (712 mg/m^3) PERC. Urinary urobilinogen levels were elevated on the 9th day of the post-exposure period. The serum glutamic-oxaloacetic transaminase (SGOT) level showed a slight increase on the 3rd and 4th days. Stewart concluded this patient had experienced marked depression of the central nervous system (CNS) followed by transient, minimal liver injury. The diagnosis of CNS depression was based on the abnormal findings of the Romberg Test. The increase in urinary urobilinogen was suggested as one indicator of hepatic injury due to PERC. Elevations in the levels of urobilinogen and other indicators of liver damage have been reported in other case studies involving acute exposures (Stewart et al., 1961a; Saland, 1967). The effects of PERC on the CNS are described in Section 6.4.

Stewart et al. (1961a) reported a case in which a male construction worker became semicomatose after being overexposed to fumes from a petroleum-based solvent, during a 3.5-hour period. Though the solvent was reported to contain 50 percent Stoddard Solvent and 50 percent PERC, Stoddard Solvent was not identified in expired air during postexposure. A neurological examination conducted one hour after collapse indicated no abnormality of function; the liver was not palpable. During a 6-week period subsequent to the incident, neither clinical jaundice nor neurological symptoms were observed. Simulated exposure conditions suggested that the estimated average concentration of PERC in the work environment, during exposure, was 393 ppm (2,666 mg/m^3). Clinical tests revealed evidence of impaired liver function, beginning 9 days following exposure; urinary urobilinogen, and total serum bilirubin were elevated. On the 14th postexposure day, urinary urobilinogen was in the normal range but a slight elevation of alkaline phosphatase was observed. Serum glutamine-pyruvic transaminase (SGPT) and SGOT values were in the normal range throughout the postexposure period, with the exception that on the 18th day, SGPT was slightly elevated. It should be noted that on the 16th postexposure day, the PERC concentration in expired air was sharply elevated. It was suggested by the investigators that such an acute exposure may represent a continuing insult to the liver in view of the observations that PERC had an exceedingly long exponential decay in expired air, indicating slow release from body tissues.

Elevated SGOT values and an enlarged liver were reported by Saland (1967). Nine firefighters were exposed to an unknown concentration of PERC upon responding to a complaint about fumes. All were exposed to levels above the odor threshold for 3 minutes without masks. There was no irritation of the eyes, mucous membranes, or respiratory tract. For some unexplicable reason, all were admitted to a hospital for study 12 days after the incident. All clinical tests indicated no abnormalities; however, 8 of 9 individuals had elevated SGOT levels. In 7 individuals, SGOT values returned to normal in 22 days after testing. Hepatomegaly and splenomegaly, were found in one individual 12 days postexposure. After 63 days postexposure, the liver was not palpable.

Nursing infants may represent a special group highly sensitive to the effects of PERC. An enlarged liver and obstructive jaundice were diagnosed by Bagnell and Ellenberger (1977) in a 6-week-old, breast-fed infant. The infant was never directly exposed to PERC vapors. The child's father worked in a dry cleaning establishment where PERC vapors were present. During regular lunchtime visits to the exposure site, the mother had been exposed to the same vapors. These visits lasted between 30 and 60 minutes. The concentration of PERC in the work place was unknown. In the infant, bilirubin, SGOT, and serum alkaline phosphatase were elevated; other blood and urinary parameters of liver function were normal. Normal liver function was found in both parents although the child's father had experienced repeated episodes of dizziness and confusion. Analysis of the mother's blood 2 hours after one of her lunchtime visits indicated a PERC level of 0.3 mg per 100 ml. Her breast milk, 1 hour after a visit, contained 1.0 mg per 100 ml. After 24 hours, the concentration of PERC in the breast milk decreased to 0.3 mg per 100 ml. Chlorinated hydrocarbons were not found in the mother's urine. One week after breast feeding was discontinued, serum bilirubin and serum alkaline phosphatase levels in the infant returned to a normal range. The findings suggest that the neonatal liver may be sensitive to toxicological effects of PERC.

Sparrow (1977) reported liver dysfunction and an increase in urinary hydroxyproline in a 19-year-old male exposed to PERC for a few minutes once a week for 4 years. Because of predisposing factors in the individual's medical history, no conclusions can be drawn regarding the effects of PERC in this case. These factors included a history of partial baldness and an absence of immunoglobulin A, which may be associated with autoimmune disease.

Levine et al. (1981) reported a diffuse and marked fatty metamorphosis of the liver of a 53-year-old male dry cleaner who succumbed to an overexposure of PERC, over an unspecified period of time. During autopsy, the PERC concentration in the liver was 240 mg/kg. PERC was also detected in blood (4.5 mg/l), brain (69 mg/kg), kidney (71 mg/kg), and liver (30 mg/kg). It was noted by the authors that the liver was extremely fatty and that an ethanol concentration of 0.20 percent (w/v) was found in the blood.

Hake and Stewart (1977) reported mild liver injury, as indicated by elevated serum enzymes, in a 60-year-old male dry cleaning operator overcome by PERC vapors. It was estimated that the individual had been lying in a pool of solvent for about 12 hours. Although kidney and skin damage also were evident, the individual was released after 21 days of hospitalization and appeared fully recovered.

6.1.1.2 Chronic--Hepatotoxic effects as a result of inhaling unknown concentrations of PERC over extended periods have been reported by a number of investigators. (Coler and Rossmiller, 1953; Franke and Eggeling, 1969; Hughes, 1954; Trense and Zimmerman, 1969; Meckler and Phelps, 1966; Larsen et al., 1977; Moeschlin, 1965; Dumortier et al., 1964) The observed effects are presented in Table 6-1. Liver function parameters observed to be altered as a

TABLE 6-1. EFFECTS OF TETRACHLOROETHYLENE ON LIVER ASSOCIATED WITH CHRONIC EXPOSURES OF HUMANS

PERC Concentration ppm	mg/m^3	Duration of Exposure	Number of Individuals Exposed	Effects	Reference
230 to 385	1,560 to 2,611	2 days/wk up to 6 yrs	4	Liver dysfunction evidenced by sulfobromophthalein retention time, serum protein patterns. One individual had cirrhosis of liver and 3+ reaction to cephalin-cholesterol flocculation test.	Coler and Rossmiller, 1953
75% of measurements less than 100 ppm (678 mg/m^3)		unknown	113	Thymol turbidity and bilirubin determinations altered.	Franke and Eggeling, 1969
unknown		12-16 hr/day often 7 day/wk 11 wk	1	Toxic hepatitis; liver function tests unspecified.	Hughes, 1954
unknown		> 1 yr	1	Individual had died of cardiovasculer failure; toxic liver cell necrosis observed upon autopsy. Chlorinated hydrocarbons not found in liver.	Trense and Zimmerman, 1969
unknown		2.5 mo	1	Hepatitis, enlarged liver, acholic stools, nausea, vomiting, jaundice of the white of the eye, and generalized itching were found. Alkaline phosphatase, SGOT, and bilirubin measurements consistent with liver disease. Liver biopsy performed 2 wk post-exposure showed degeneration of parenchymal cells, exaggeration of sinosoids and focal collections of mononuclear cells - liver still enlarged after 6 wk post-exposure.	Meckler and Phelps, 1966
unknown		unknown	1	Woman had worn clothing which had been dry-cleaned. Admitted to hospital in comatose state with grand mal seizure. Bilirubin, SGOT and LDH elevated. Renal insufficiency also evident. SGOT and LDH returned to normal during hospitalization.	Larsen et al., 1977

TABLE 6-1 (continued).

PERC Concentration		Duration of Exposure	Number of Individuals Exposed	Effects	Reference
ppm	mg/m^3				
unknown		unknown	1	Male had worn clothing which had been dry-cleaned. Initial symptoms were abdominal pain and blood-tinged vomiting. SGOT increased 4 to 5 times normal 1 day after initial symptoms. Jaundice of eye and enlarged liver were not detected. SGOT returned to normal. Serum bilirubin normal throughout diagnosis.	Ibid.
unknown		6 yr	1	Liver dysfunction; returned to normal 20 days after cessation of exposure.	Moeschlin, 1965
unknown		unknown	1	Enlarged liver; patient had history of alcoholism.	Dumortier et al., 1964
59 to 442	400 to 3,000	unknown	25	Increases in serum aminotransferases; decreased activity of cholinesterase presumably as a result of damage to liver cells.	Chmielewski et al., 1976

result of PERC exposure include sulfobromophthalein retention time, thymol turbidity, serum bilirubin, serum protein patterns, cephalin-cholesterol flocculation, serum alkaline phosphatase, SGOT, and serum lactic acid dehydrogenase (LDH).

Effects observed included cirrhosis of the liver (Coler and Rossmiller, 1953), toxic hepatitis (Hughes, 1954; Meckler and Phelps, 1966), liver cell necrosis (Trense and Zimmerman, 1969; Meckler and Phelps, 1966), and enlarged liver (Meckler and Phelps, 1966). In some cases, liver dysfunction parameters returned to normal following cessation of exposure (Hughes, 1954). In one case, the liver was enlarged 6 months after cessation of exposure (Meckler and Phelps, 1966).

Liver dysfunction was evidenced in a 24-year old male who was admitted to the hospital with abdominal pains and blood-tinged vomitus (Larsen et al., 1977). This individual, 3 days before hospitalization, was exposed to PERC vapors emanating from recently drycleaned clothes. In this study, SGOT values increased 4 to 5 times above normal 1 day after initial symptoms. Two days later, SGOT returned to a normal range. He was found to have renal insufficiency and mild proteinuria. Despite diureses, serum creatinine and blood area increased constantly. Serum bilirubin was normal throughout hospitalization. Variations in the levels of SGOT and other liver function parameters during the postexposure period indicate that repeated testing during this interval is required for complete diagnosis.

Larsen et al. (1977) also described an incident in which a female drycleaning worker who was hospitalized in a comatose state with a grand mal seizure. Three days prior to hospitalization she had worn clothing that had been recently drycleaned. Upon admission, SGOT and serum LDH levels were reported to be strongly elevated; levels gradually decreased during hospitalization. Blood and protein were found in the urine. Elevated serum creatinine levels decreased after peritoneal dialysis. While PERC may have contributed to the coma and seizure, this cause-effect relationship is unproven.

Chmielewski et al. (1976) found that the activities of alanine and asparagine aminotransferase were significantly elevated ($t_{0.05} = 2.032$) in a group of 16/25 workers compared to non-exposed controls. This group of 16 workers had been exposed to PERC vapors in the range of 59 to 442 ppm (400 to 3,000 mg/m^3) for periods ranging from 2 months to 27 years. Aminotransferase activity in a group of 9 workers exposed to levels of PERC at or below 29 ppm (200 mg/m^3) was normal. These enzyme imbalances were indicative, to the investigators, of liver cell damage by PERC. Low urinary excretion of 17-ketosteroids (11/25 cases) and abnormal EEG tracings (4/16 cases) in the high exposure group also were observed by the investigators.

6.1.2. Effects on Kidneys

Diminished excretion of urine (5 to 10 ml urine per hour), uremia, and elevated serum creatinine was observed in a woman exposed to PERC vapors emanating from clothes that had been drycleaned (Larsen et al., 1977). As previously described, she had been admitted to the hospital in a comatose state with a grand mal seizure. During hospitalization, diuresis and serum creatinine returned to normal. Renal biopsy suggested toxic nephropathy. Liver dysfunction also was evidenced by increased SGOT and bilirubin levels (section 6.1.1). Protein and blood were detected in the urine.

In another situation in which an individual (male) had worn clothing permeated with PERC vapors, elevated serum creatinine and blood uremia was observed (Larsen et al., 1977). This individual was admitted to the hospital with abdominal pains and blood-tinged vomiting. Mild proteinuria and leukocytes and erythrocytes were found in the urine. Despite diuresis, serum creatinine and blood urea increased. Serum creatinine decreased with peritoneal dialysis, over a 19-day treatment period. Renal biopsy evidenced necrosis in the renal tubules.

Advanced membranous nephropathy was diagnosed by Ehrenreich et al. (1977) in an individual who had been exposed to PERC and other solvent vapors for more than 15 years. [Membranous nephropathy is a chronic renal disease involving glomeruli and occurs principally in adults (Ehrenreich and Churg, 1968)]. A mild proteinuria (1 to 2 g/day) and a slightly elevated blood pressure persisted, upon patient improvement with steroid treatment.

A co-worker of the above individual, exposed to various solvents for 11 years developed kidney, heart, and respiratory difficulties. He became ill, lapsed into a coma, and died of severe acidosis. Upon autopsy, indications of membranous nephropathy were found. However, a causal relationship with solvent exposure was not established.

Hake and Stewart (1977) reported renal damage, indicated by a proteinuria which lasted 20 days and hematuria for 8 days, in a 60-year-old male dry cleaning worker who was overcome by PERC vapors. Liver damage (section 6.1.1.2) and skin damage (6.1.3.3) also were reported. The individual was reported fully recovered upon release, after 21 days, from the hospital.

6.1.3. Effects on Other Organs/Tissues

6.1.3.1 Effects on the Pulmonary System--A 7-hour occupational exposure of a male to an unknown concentration of PERC produced findings consistent with acute pulmonary edema (Patel et al., 1977). Bubbling rales were heard over the entire lung field. Complete recovery was made 4 days after hospital admission. Liver and kidney function tests in this patient were normal.

Levine et al. (1981) reported pulmonary damage in a 53-year-old male dry cleaner who succumbed upon overexposure to PERC vapors. Findings, upon autopsy, were congestion superimposed on mildly fibrotic and diffusely emphysematous lungs with apical bullous emphysema. The PERC concentration in lung tissue was 30.0 mg/kg. A co-worker, also overcome by vapors, was reported to have recovered without complications after hospitalization. The PERC concentration in the workplace air at the time of the incident was not reported.

6.1.3.2 Hematological Effects--Alkaline phosphatase in leukocytes is a defense mechanism against bacterial infection and plays an active part in phagocytosis. In an investigation of the effects of PERC on alkaline phosphatase activity in human neutrophilic leukocytes, Friborska (1969) found that activity was within the normal range. In this study of occupational exposure, seven workers were exposed to PERC and four had been exposed to both PERC and trichloroethylene. For controls, 20 unexposed individuals were used. Trichloroethylene exposure, as opposed to PERC, raised the activity of the alkaline phosphatase above the control level. For those individuals exposed to both compounds, no synergistic or additive effect was observed.

A slight depression in the total white blood cell count of 3 of 9 firemen exposed for 3 minutes to unknown concentrations of PERC was reported by Saland (1967). The white cell count was made 12 days after the firemen were exposed to PERC.

6.1.3.3 Effects On The Skin--The effects of PERC upon the skin range from a mild to moderate burning sensation when in direct contact for 5 to 10 minutes, to a marked erythema, and finally blistering (Hake and Stewart, 1977).

Stewart and Dodd (1964) reported that individuals experienced a mild burning sensation on their thumbs after immersion of the thumbs in a solution of PERC for 5 to 10 minutes. After the thumbs were withdrawn, burning persisted without a decrease in intensity for 10 minutes before gradually subsiding after 1 hour. A marked erythema was present in all cases and subsided between 1 and 2 hours post-exposure.

Morgan (1969) reported erythema and blistering over 30 percent of the body of a worker anesthetized for thirty minutes upon overexposure in a coin-operated laundry.

Ling and Lindsay (1971) reported severe burns when an individual, upon losing consciousness, fell into a pool of PERC on the floor. The burns gradually healed within 3 weeks following exposure.

6.1.4. Behavioral and Neurological Effects

In nearly all the occupational situations involving short-term exposures to PERC, an initial characteristic response is depression of the CNS. Subchronic exposures produce characteristics of a neurasthenic syndrome; the most frequently reported subjective complaints are dizziness, headache, nausea, fatigue, and irritation of the eyes, nose, and throat; individuals may vary greatly in sensitivity. Long-term exposures have been reported to result in exacerabated symptoms or more serious behavioral and neurological findings.

6.1.4.1 Effects of Short-Term Exposures--Stewart (1969) reported normal neurological findings, except for the Romberg test, in an individual who had been exposed to approximately 105 ppm (712 mg/m^3) for less than 30 minutes. The Romberg test is designed to detect swaying motions when the subject stands with eyes closed. Upon return to work, the individual reported being very fatigued after 4 hours of light work. It was suggested that abnormal results of the Romberg test are the earliest indications of signs of intoxication due to PERC. In another study, Stewart (1961b) reported that lightheadedness was experienced when sedentary individuals were exposed to 101 ppm for 83 minutes.

Rowe et al. (1952) reported that six individuals exposed to an average PERC concentration of 106 ppm (719 mg/m^3) (range = 83 to 130 ppm; 663 to 881 mg/m^3) did not evidence CNS effects. At an average PERC concentration of 216 ppm, (1,465 mg/m^3) four of four individuals exposed for 45 minutes to 2 hours experienced slight eye irritation, developing 20 to 30 minutes into the exposure period. Minimal, transient eye irritation was noted which led the authors to suggest that the vapor concentration causing this effect in unacclimatized individuals lies between 100 and 200 ppm (678 and 1,356 mg/m^3). Dizziness and sleepiness also were noted. Recovery from all symptoms was complete within an hour after exposure. An exposure to an average concentration of 280 ppm (1,899 mg/m^3) for up to 2 hours resulted in complaints of lightheadedness, burning sensation in the eyes, congestion of frontal sinuses, and tightness about the mouth. Transient nausea was reported by one individual. The subjects felt that motor coordination was impaired and mental effort was required for coordination. Motor coordination was accomplished only with mental effort when two individuals were exposed to an average PERC concentration of 600 ppm (4,070 mg/m^3). Recovery was complete within an hour after exposure. An average exposure concentration of 1,060 ppm (7,190 mg/m^3) for 1 minute was intolerable to three of four individuals. None experienced functional disturbances. Recovery was rapid.

No behavioral or neurological effects were reported by Carpenter (1937) when four individuals were exposed to 500 ppm PERC for 70 minutes. Short-term exposures to higher concentrations resulted in reports by subjects of mental fogginess, lassitude, inebriation, loss of inhibition, and vertigo. At an exposure level of 1,500 ppm (10,174 mg/m^3), shortness of breath, nausea, mental sluggishness, and difficulties in maintaining balance were reported during the post-exposure period. Tinnitus, ringing of the ears, was reported upon exposure to 2,000 ppm (13,565 mg/m^3) for 7.5 minutes.

Weichardt and Lindner (1975) recorded subjective responses of headaches, giddiness, numbness, alcohol intolerance, intolerance of fats and fried foods as a result of exposures to between 11 to 45 ppm (75 to 305 mg/m^3) for approximately 3 hours.

In a case study involving a nursing mother exposed daily for 30 to 60 minutes to unknown PERC concentrations, Bagnell and Ellenberger (1977) recorded subjective complaints of dizziness.

6.1.4.2 Long-term Effects--In a comprehensive 3-month chamber study of 6 males and 6 females designed to elicit interactions between ethanol and diazepam (Valium®) and PERC, Stewart and coworkers (Stewart et al., 1977; Hake and Stewart, 1977) found that exposure to 25 and 100 ppm (170 and 678 mg/m^3) PERC alone had no effect on the electroencephalogram (EEG) tracings. A slight but statistically significant detrimental effect upon the Flanagan coordination test was repeatedly found at an exposure level of 100 ppm (678 mg/m^3). This test requires subjects to follow a spiral pathway with a pencil, touching the sides of the pathway as few times as possible.

Each subject was exposed 5.5 hours daily. The exposure duration was 11 weeks. Monday and Tuesday were generally control days. Thursday was an intermediate exposure day. Wednesday and Friday were 100 ppm exposure days. No other unusual behavioral or neurological finding were noted upon exposures to PERC alone. Subjective complaints were noted, however; one subject accounted for one-third the incidence of headache and two-thirds the incidence of nausea reported by the nine subjects who completed the study. The absence of EEG abnormalities, such as were found in an earlier study by Stewart and co-workers (1974) suggest that EEG observations may not be reliable indicators of early signs of PERC narcosis. In their earlier study, impairment of coordination was occasionally noted during exposures to 150 ppm for 7.5 hours. It should be noted that Chielewski et al. (1976) observed abnormal EEG tracings in 4/16 individuals exposed occupationally, from 2 months to 27 years, to 59 to 442 ppm (400 to 3,000 mg/m^3).

Hake and Stewart (1977) reported decrements in coordination as measured by the Flanagan coordination test when males had been exposed to both 100 ppm and 150 ppm (678 and 1017 mg/m^3) for 7.5 hours/day for five weeks. Scores were significantly decreased on at least one day during the weeks of 100 ppm (678 mg/m^3) and 150 ppm (1017 mg/m^3) exposure. Only traces of trichloroacetic acid were measured in 24-hour urine collections during these exposures. Trichloroethanol was not found.

Stewart et al., (1970) noted subjective complaints of headaches (25 percent), eye, nose, or throat irritation (60 percent), sleepiness (40 percent), and lightheadedness in individuals exposed to 101 ppm for 7 hours. One-quarter of the individuals had difficulty in speaking. Upon repeated exposures to this level, mild eye and throat irritation were consistently reported by two of five test subjects. Abnormal Romberg test findings in three individuals were recorded within the first 3 hours of exposure. During the post-exposure period, repeat tests were normal. All other neurological test results were normal.

Similar subjective complaints, as well as neurological effects, of PERC also were recorded in other studies (Method, 1946; Lob, 1959; Eberhardt and Freundt, 1966; Gold, 1969).

6.1.5 Epidemiological Findings

Several epidemiological studies, concerning PERC, have been conducted. These studies, focussing upon occupational exposure situations, both in the United States and in Europe, provide valuable information relating to the effects of this chemical. Details concerning these studies can be found in The Carcinogen Assessment Group (CAG) report, attached as an appendix (pp. 42-45).

6.1.5.1 NIOSH Study--The National Institute for Occupational Safety and Health (NIOSH) contracted for a retrospective cohort study of mortality among dry cleaning industry workers exposed to PERC for at least one year prior to 1960. The information available is in the form of an unpublished report to NIOSH (Kaplan, 1980). As detailed in the CAG report, no conclusions can be drawn from this study because of incomplete follow-up, the short observation period of no more than 18 years, and the potential bias because confounding variables were not sufficiently controlled.

6.1.5.2 National Cancer Institute--In this proportionate mortality study of laundry and dry cleaning workers who had been exposed to various solvents, preliminary findings suggest an increased risk for malignant neoplasms (Blair, et al., 1979). Limitations of the study are discussed in the CAG report.

6.1.5.3 Oklahoma University--Preliminary results of a study assessing cause of death of dry cleaning workers in Oklahoma suggest increased death from kidney cancer in male workers. Results are unpublished.

6.1.5.4 Wisconsin Study--Katz and Jowett (1981) reported that a mortality analysis of 671 white female laundry and dry cleaning workers for the period 1963-1977 failed to show an overall increase in malignant neoplasms. A proportionate mortality ratio was calculated, from data obtained from death certificates, using the classification of both all occupations and lower wage occupations, as controls. An elevated proportionate mortality ratio for cancer of the kidney ($p<0.05$) and genitals ($p<0.05$) was found, using both control classifications.

The failure to find an elevated risk for the classification of all malignant neoplasms is in contrast to the findings of Blair et al., (1979). This discrepancy was suggested as possibly being due to differences in study design. It was noted that in other areas of the country, non-white dry cleaning workers constitute a larger percentage of the work force. The absence of data regarding duration of employment together with the inability to distinguish between laundry and dry cleaning workers necessitates a cautious interpretation of the data.

6.2 ANIMAL

Reported toxic effects associated with tetrachloroethylene (PERC) exposure in laboratory animals include effects on the central nervous system (CNS), cardiovascular system, skin, liver, kidney, and the immune system.

A number of recent reviews (NIOSH, 1976; Fuller, 1976; USEPA, 1980; Walter, et al., 1976; Parker et al., 1978; Fishbein, 1976; USEPA, 1977) support the assessment of the toxic effects of tetrachloroethylene in animals as presented below. Summaries of these toxic effects and of toxic dose data also appear in Tables 6-2 and 6-3.

6.2.1 Effects on the Nervous System

Acute effects of PERC are very much dominated by CNS depression. Abnormal weakness, handling intolerance, intoxication, restlessness, irregular respiration, muscle incoordination, and unconsciousness are among the symptoms, considered to be manifestations of effects on the CNS, which have been observed in exposed animals.

Symptoms of acute CNS depression have been seen in experimental animals (NIOSH, 1976; Fuller, 1976; USEPA, 1980; Walter et al., 1976; Parker et al., 1978; Fishbein, 1976; USEPA, 1977) and in dogs treated with therapeutic (antihelmintic) doses (Miller, 1966; Snow, 1973; Christensen and Lynch, 1973) of PERC.

Rowe et al. (1952) reported that behavioral changes were not observed in rats, guinea pigs, rabbits, or monkeys exposed repeatedly for 7 hours a day at vapor concentrations of PERC up to 401 ppm (2,720 mg/m^3).

TABLE 6-2. SUMMARY OF THE EFFECTS OF TETRACHLOROETHYLENE ON ANIMALS

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rabbits (female)		(skin)	single application single installation (eye)	primary eye and skin irritant	Duprat et al., 1976
Rabbit	13 m mole/ kg	oral	single dose	marked increase in serum enzymes i.e., alkaline phosphatase, SGOT, and SGPT within 24 hours	Fujii et al., 1975
Mice	200 ppm	inhalation	4 hours single exposure	moderate fatty infiltration of the liver 1 day after exposure but not 3 days after	Kylin et al., 1963
Mice	200 ppm	inhalation	4 hours/day 6 days/week 1-8 weeks	fatty degeneration of the liver	Kylin et al., 1965
Guinea pigs	100 ppm	inhalation	7 hours/day 5 days/week 132 exposures	increased liver weights in females	Rowe et al., 1952
Guinea pigs	200 ppm	inhalation	7 hours/day 5 days/week	increased liver weights with some fatty degeneration in both males and females - slight increase in lipid content, and several small fat vacuoles in liver	Rowe et al., 1952

TABLE 6-2 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Guinea pigs	400 ppm	inhalation	7 hours/day 5 days/week 169 exposures	more pronounced liver changes than at 200 ppm slight cirrhosis was observed - increased liver weight, increase in neutral fat and esterified cholesterol in the liver, moderate central fatty degeneration, cirrhosis	Rowe et al., 1952
Guinea pigs	2,500 ppm	inhalation	18 7-hour exposures	loss of equilibrium, coordination and strength increase in weights of liver and kidney, fatty degeneration of the liver, cloudy swelling of tubular epithelium of the kidney	Ibid.
Rabbits Rats Monkeys	100-400 ppm	inhalation	7 hours/day 5 days/week 6 months	no abnormal growth, organ function or histopathologic findings	Ibid.
Rabbits	2,500 ppm	inhalation	28 7-hour exposures	central nervous system (CNS) depression without unconsciousness	Ibid.
Rat	2,500 ppm	inhalation	1-13 7-hour exposures	loss of consciousness and death	Ibid.
Rat	1,600 ppm	inhalation	18 7-hour exposures	drowsiness, stupor, increased salivation, extreme restlessness, disturbance of equilibrium and coordination, biting and scratching reflex	Ibid.

TABLE 6-2 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rat	3,000-6,000	inhalation	single exposure up to 8 hours	increase in liver weight, increase in total lipid content of liver accompanied by a few diffusely distributed fat globules	Ibid.
Rabbit	15 ppm	inhalation	3-4 hours/day 7-11 months	depressed agglutinin formation	Mazza 1972
Rabbit	2,212 ppm (15 mg/l)	inhalation	45 days 4 hrs/day 5 days/week	liver damage indicated by elevated SGPT, SGOT, SGLDH: marked reduction of Schmidt index	Ibid.
Rats	70 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	no pathological findings	Carpenter 1937
Rats	230 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	similar, but less severe pathological findings as with 470 ppm - congestion and light granular swelling of kidneys	Carpenter 1937
Rats	470 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	congested livers with cloudy swelling, no evidence of fatty degeneration or necrosis: evidence of kidney injury - increased secretion, cloudy swelling and desquamation of kidneys: congestion of spleen	Ibid.
Rats	2,750-9,000 ppm	inhalation	single exposure	no deaths	Ibid.

TABLE 6-2 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rats	19,000 ppm	inhalation	30-60 minutes	congested livers with granular swelling, some deaths	*Ibid*.
Rabbits	15 ppm	inhalation	3-4 hours/day 7-11 months	moderately increased urinary urobilinogen, pathomorphological changes in the parenchyma of liver and kidneys	Navrotskii et al., 1971
Rabbit	2,211 ppm (15 mg/l)	inhalation	45 days	significant reduction of glomerular filtration rate and the renal plasma flow; decrease of highest excretory tubular capacity (kidney damage)	Brancaccio et al., 1971
Mice (Swiss) Male 10 Animals	2.5 ml/kg	i. p.		100 mg percent or more protein found in 1 of 6 mice - proximal convoluted tubules were swollen in all animals and necrotic in one	Plaa & Larson, 1965
10 Animals	5.0 ml/kg	i.p.		2 of 4 mice had 100 mg percent or more protein in urine	

(urine samples were collected 24-hours post-injection)

TABLE 6-2 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rabbit	2,211 ppm (15 mg/l)	inhalation	45 days	increased plasma and urine levels of adrenal cortical and adrenal medullar hormones; increased excretion of principal catecholamine metabolite (not statistically significant)	Mazza & Brancaccio, 1971
Mouse		i. p.		liver dysfunction	Klassen & Plaa, 1966
Mouse		i. p.		LD_{50}	Ibid.
Dog		i. p.		caused significant liver dysfunction indicated by elevated SGPT	Klaasen & Plaa, 1967
Dog	i. p.			caused PSP (phenolsulfonephtalein) retention indicating kidney dysfunction	Klassen & Plaa, 1967
Dog	i. p.			LD_{50} in dog	Ibid.
Rats	300 ppm	inhalation	7 hours/day days 6-15 of gestation	decreased maternal weight gains, increased fetal reabsorptions	Schwetz, et al., 1975
Mice	300 ppm	inhalation	7 hours/day days 6-15 of gestation	maternal liver weights increased relative to body weight; increased incidences of fetal subcutaneous edema, delayed ossification of skull bones, and split sternebrae	Ibid.

TABLE 6-2 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Rat	44.2 ppm	inhalation	entire gestation period	decreased levels of DNA and total nucleic acids in the liver, brain, ovaries, and placenta	Aninina 1972
Mouse	15-74 ppm	inhalation	5 hours/day 3 months	decreased electroconductance of muscle and "amplitude" of muscular contraction	Dmitrieva, 1968
Rats	15 ppm	inhalation	4 hours/day 5 months	EEG changes and protoplasmal swelling of cerebral cortical cells, some vacuolated cells and signs of karyolysis	Dmitrieva, 1966
Rats	73 and 147 ppm	inhalation	4 hours/day 4 weeks	EEG and electromyogram changes; decreased acetylchlolinesterase activity	Dmitrieva, 1966
Dogs (male beagles)	0.5-1.0% v/v 5,000 & 10,000 ppm	inhalation	7 min house air followed by 10 minutes tetrachloroethylene 8 μg/kg Epinephrine given I.V. (1) a control dose after 2 min of breathing air (2) challenge dose after 5 min of breathing test compound	cardiac sensitization (development of serious arrhythmia or cardiac arrest) was not induced at the concentrations tested (other similar compounds gave positive results at same concentration)	Reinhardt et al., 1973
Cats	3,000 ppm	inhalation	4 hours	no anesthesia	Lehmann, 1911
Cats	14,600 ppm	inhalation	1-2 hours	anesthesia	Lehmann and Schmidt-Kehl, 1936

TABLE 6-2 (continued).

Animal Species	(Conc) Dose	Route	Exposure Variables	Effects	Reference
Mouse	40 mg/l 5,900 ppm	inhalation		minimal fatal concentration	Lamson et al.,1929
Mouse	4-5 ml/kg	oral		death in 2-9 hours from CNS depression	*Ibid.*
Rabbit	5 ml/kg	oral in oil		death in 17-24 hours	*Ibid.*
Cat	4 mg/kg	oral in oil		death within hours	*Ibid.*
Dog	9,000 ppm	inhalation		narcosis, marked salivation, "narrow margin of safety"	*Ibid.*
Dog	4-25 ml/kg	oral in oil		death in 5-48 hours	*Ibid.*

TABLE 6-3. TOXIC DOSE DATA

Description of exposure	Species	Route of administration	Dose (conc)	Toxic effect endpoint	Time	Reference
LD_{50}	male mouse	oral	8100 mg/kg	death	36 hr.	Wenzel & Gibson
LD_{50}	mouse	i.p.	2.9 ml/kg 28 mM/kg 4700 mg/kg	death	24 hr.	Klaasen & Plaa, 1966
ED_{50}	mouse	i.p.	2.9 ml/kg 28-32 mM/kg	liver dysfunction		
LD_{50}	mouse	i.p.	34 mM/kg	death	24 hr.	Gehring 1968
ED_{50}	mouse	i.p.	24 mM/kg	liver toxicity		
LD_{50}	dog	i.p.	2.1 ml/kg 21 mM/kg 3400 mg/kg	death	24 hr.	Klaasen & Plaa, 1967
ED_{50}	dog	i.p.	0.74 ml/kg 7.2 mM/kg	liver damage	24 hr.	*Ibid*.
ED_{50}	dog	i.p.	1.4 ml/kg	kidney dysfunction	24 hr.	*Ibid*.
LD_{50}	mouse	subcutaneous	390 mM/kg	death	10 da.	Plaa et al., 1958
ED_{50}	mouse	subcutaneous	27 mM/kg	liver toxicity		*Ibid*.

TABLE 6-3 (continued).

Description of exposure	Species	Route of administration	Dose (conc)	Toxic effect endpoint	Time	Reference
LD_{50}	mouse	oral (undiluted)	0.109 ml	death		Dybing and Dybing, 1946
LD_{50}	mouse	oral (in oil)	0.134 ml	death		Ibid.
LD_{50}	mouse	oral	8850 mg/kg	death		Handbook of Toxicology, W. B. Saunders, 1959
*LCLo	mouse	inhalation	23000 mg/m^3	death	2 hr.	
LD_{50}	rat			death		Withey & Hall, 1975
$^{*}LCL_{o}$	rat	inhalation	4000 ppm	death	4 hr.	Handbook of toxicology, 1959
$^{*}LCL_{o}$	rat	inhalation	4000 ppm	death	4 hr.	
$^{**}LDL_{o}$	dog	oral	4000 mg/kg	death		Archivfuer Hyg. Bakteriol. 116:131, 1936
$^{**}LDL_{o}$	dog	i.v.	85 mg/kg	death		Carpenter et al., 1949

TABLE 6-3 (continued).

Description of exposure	Species	Route of administration	Dose (conc)	Toxic effect endpoint	Time	Reference
**LDL_o	cat	oral	4000 mg/kg	death		Clayton, 1962
**LDL_o	rabbit	oral	5000 mg/kg	death		Lamson et al., 1929

*LCL_o - lethal concentration low the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in humans or animals.

**LDL_o - lethal dose low the lowest dose of a substance other than an LD_{50} introduced by any route other than inhalation over any given period of time and reported to have caused death in humans or animals introduced in one or more divided portions.

A single 4-hour exposure to 2,270 ppm (15,400 mg/m^3) PERC caused rats to suffer an 80 percent loss of both avoidance and escape responses (Goldberg et al., 1964). Savolainen et al. (1977) demonstrated behavioral impairment in rats exposed to 200 ppm (1,357 mg/m^3) PERC vapor 6 hours a day for 4 days. Marked increases in the frequency of ambulation in the open field were most significant 1 hour after exposure when compared to controls. High tissue concentrations of PERC were reached in fat and brain from a relatively short exposure. A significant decrease in the ribonucleic acid (RNA) content of the brain was measured as well as an increase in nonspecific cholinesterase activity.

Encephalography was utilized to study the action of PERC during long-term exposure of rats (Dmitrieva, 1966; Dmitrieva and Kuleshov, 1971; Dmitrieva et al., 1968; Dmitrieva, 1973; Dmitrieva, 1968). Alterations in EEG patterns were associated with increased electrical impedence of the cerebral cortex at exposures as low as 15 ppm (102 mg/m^3), 3 to 4 hours/day for 7 to 11 months. In the study by Dmitrieva and Kuleshov (1971), rats exposed to 1.5 ppm (10.2 mg/m^3) showed no effect of treatment. Histologic examination revealed sporadic swollen cortical cells, and some of which exhibited vacuolized protoplasm. These interacting changes in the bioelectrical activity and electric conductivity of the brain in rats exposed to PERC are indications of long-term effects on the CNS. It should be noted, however, that in these experiments the number of animals in each exposure was small (14 to 15 animals) and statistical analyses were not reported. In the report by Dmitrieva and Kuleshov (1971), the EEG patterns rapidly reverted to normal after cessation of exposure. In rats exposed to 1.5 ppm (10.2 mg/m^3), no effects of exposure was observed.

6.2.2 Effects on the Liver and Kidney

Tetrachloroethylene is generally regarded as being both hepatotoxic and nephrotoxic.

Carpenter (1937) exposed three groups of 24 albino rats each to PERC vapor concentrations averaging 70, 230, or 470 ppm (475, 1,560, or 3,188 mg/m^3) for 8 hours/day, 5 days/week, for up to 7 months. The maximum exposure for any animal during the 7 month period was 150 days (1,200 hours). A group of 18 unexposed animals served as controls.

The rats exposed to 470 ppm (3,188 mg/m^3) for 150 days, followed by a 46-day rest period, developed cloudy and congested livers with swelling; there was no evidence of fatty degeneration or necrosis. These rats also had increased renal secretion with cloudy swelling and desquamation of kidneys, as well as congested spleens with increased pigment. The pathologic changes were similar but less severe in the rats exposed to 230 ppm (1,560 mg/m^3). In some instances, there was congestion and light granular swelling of the kidneys after 21 exposure days. After 150 days of exposure, followed by a 20-day rest, congestion was found in the kidneys and in the spleens. The livers showed reduced glycogen storage. Microscopic evidence of damage to liver, kidney, or spleen in rats exposed at 70 ppm (475 mg/m^3) for 150 days was not observed. In addition, microscopic examination of heart, brain, eye, or nerve tissue did not reveal any damaging effects in any of the chronically exposed rats. Functional parameters, including icteric index, Van den Bergh test for bilirubin, and blood and urine analysis, were normal after the exposures. Fertility of female rats, as measured by a fertility index (actual number of litters/possible number of litters), was increased slightly after repeated exposures to 230 or 470 ppm (1,560 or 3,188 mg/m^3) PERC. No deaths or signs of anorexia or diminished activity was observed during the chronic exposures.

Carpenter also tried to determine the highest concentration of PERC vapor that would not anesthetize rats exposed for 8 hours. Exposure to 31,000 ppm

(210,273 mg/m^3) was lethal within a few minutes. Rats exposed to 19,000 ppm (128,871 mg/m^3) died after 30 to 60 minutes. Animals exposed to 19,000 ppm (128,877 mg/m^3) but removed from the inhalation chamber just prior to unconsciousness, developed congestion and granular swelling of the liver. Similar liver effects were seen after exposure at 9,000 ppm (61,047 mg/m^3). There was also marked granular swelling of the kidneys. A single exposure at 9,000, 4,500, or 2,750 ppm (61,047, 30,523, or 15,261 mg/m^3) did not cause death to any of the rats in this study; however, post-mortem examinations of the rats exposed to those concentrations revealed a slight increase in the prominence of liver and kidney markings.

Rowe et al. (1952) exposed rabbits, monkeys, rats, and guinea pigs to PERC vapor for 7 hours, 5 days/week for up to 6 months. Exposure concentrations ranged from 100 to 2,500 ppm (678 to 16,957 mg/m^3). Three of the four species tested -- rabbits, monkeys, and rats -- showed no effects of repeated exposures to concentrations up to 400 ppm (2,713 mg/m^3). There were no adverse effects on growth, liver weight or lipid content, gross or microscopic anatomy observed in any animal. In contrast, guinea pigs showed marked susceptibility to PERC in this study. The liver weights of female guinea pigs increased significantly after 132 seven-hour exposures at 100 ppm (678 mg/m^3). At 200 ppm (1,356 mg/m^3), there was a slight depression of growth in female guinea pigs and increased liver weights in both males and females. Slight to moderate fatty degeneration of the liver also was observed. These effects were more pronounced in guinea pigs that received 169 7-hour exposures at 400 ppm (2,713 mg/m^3). At this concentration, there also were increased amounts of neutral fat and esterified cholesterol in livers. Gross and microscopic examination of the tissues revealed slight to moderate fatty degeneration in the liver with slight cirrhosis. Rowe et al. stated that at 395 ppm (2,680 mg/m^3)

increased kidney weights also were observed in guinea pigs but not in other species.

Klaasen and Plaa (1967) showed that intraperitoneal (i.p.) injections of PERC to mongrel male and female dogs can produce damage to kidney and liver. They estimated the ED_{50} (effective dose in 50 percent of the animals tested) for liver and kidney damage as well as the 24-hour LD50 value (lethal dose in 50 percent of the animals treated). The ED_{50} values were measured by sulfobromophthalein (BSP), SGPT, glucose, protein, and phenolsulfonephthalein (PSP) indicators of liver or kidney dysfunction. The LD_{50} was 2.1 ml/kg (21 mmoles/kg) and the ED_{50} for elevation of SGPT was 0.74 ml/kg (7.2 mmoles/kg). The ED_{50} for diminution of PSP excretion was 1.4 ml/kg (14 mmoles/kg). After administration, effects on the liver and kidneys were determined by microscopic examination. At near-lethal doses, PERC produced moderate neutrophilic infiltrations in the sinusoids and portal areas; necrosis was not observed. Near the ED_{50}, vacuolization of centralobular hepatocytes in about half the animals was observed. After a single i.p. injection at 0.75 x LD_{50}, SGPT peaked at 2 days and rapidly declined throughout the 9-day measurement period. Kidney dysfunction was deemed significant when PSP excretion was < 39 percent (determined 24 hours after i.p. injection). At near PSP excretion--ED_{50} doses, only mild dilation of the collecting ducts were seen in some of the kidneys.

In a similar study using Swiss-Webster mice, Klaasen and Plaa (1966) determined that the 24-hour LD_{50} was 2.9 ml/kg (28 mmoles/kg). The ED_{50} for BSP retention was 2.9 ml/kg (32 mmoles/kg). The ED_{50} for elevation of SGPT was 2.9 ml/kg (28 mmoles/kg). When ethanol (5 gm/kg) was administered by gavage for 3 days prior to injection of 1.0 ml/kg PERC, neither PSP excretion nor BSP retention was significantly altered. At BSP-ED_{50} doses, mice exhibited predominantly inflammatory changes with trace to marked quantities of lipid accumulation.

Agglutinin production, clinical chemistry, and histologic changes in liver and kidney were examined by Navrotskii (1971) in rats and rabbits exposed for 7 to 11 months to PERC at 15 ppm (102 mg/m^3), 1.5 ppm (10.2 mg/m^3) and 0.3 ppm (2.0 mg/m^3). Exposure was conducted as reported in the study by Dmitrieva and Kuleshov (1971). The number of animals and whether the results applied to rats or rabbits or both was not apparent in the report. At 15 ppm (102 mg/m^3), agglutinin production was decreased 2.7 to 7.6 times (the data for individual chlorinated compounds was not separated). Although it was reported that PERC had an effect on antibody titers at 1.5 ppm (10.2 mg/m^3), there was no effect of treatment at 0.3 ppm (2 mg/m^3). Phagocytic activity was reported to be increased by 15 to 30 percent over controls after exposure (1 to 1.5 months) to 1.5 ppm (10.2 mg/m^3). No histologic changes in liver and kidney of animals at any dose level were observed. Fluctuations in clinical chemistry parameters were observed but there was not indication of any significant change; data pertaining to PERC were described but not reported. Navrotskii and coworkers (1971) concluded that chronic exposure to 15 ppm (102 mg/m^3) PERC is the "minimum active concentration" necessary to observe a biological effect.

Similar results in rabbits exposed to 15 and 1.5 ppm (102 and 10.2 mg/m^3) PERC for 3 hours per day, for 8 to 10 months, were reported by Schmuter (1972).

Effects upon the liver of rats exposed continuously for 3 months to 0.7 and 2.7 ppm (4.5 and 19 mg/m^3) were reported by Bonashevskaya (1977b). In the low exposure group, an increase in the activity of succinate dehydrogenase (SDH) was reported. At the high level, SDH was slightly decreased in the central lobular sections while activity in the peripheral zones was either unchanged or increased. The activities of glucose-6-phosphate dehydrogenase (G6PDH) were similar in pattern to that for SDH. RNA content was reported to be decreased. Lactic dehydrogenase (LDH) activity was either unchanged or increased. The enzyme variations were indicative to the author of adaptation to exposure. No significant histomorphological changes in the liver were reported at either exposure level.

A subcutaneous injection (0.4 ml daily, for 8 weeks) of PERC to groups of rats fed on high protein diets have a protective effect upon the liver (Dumitrache et al., 1975). PERC was observed to induce liver hypertrophy compared to controls ($p < 0.001$). Hypertrophy was most pronounced in the low protein group. In treating rats fed the low protein diets, cholesterol was elevated ($p < 0.001$) as well as total liver lipids ($p < 0.001$) compared to controls. Twelve rats were used in each of the four groups.

Kylin et al. (1963) noted moderate fatty degeneration of the liver with a single 4-hour exposure to 200 ppm (1,356 mg/m^3) PERC in female albino mice, sacrificed 1 day after exposure. Degeneration was not observed in mice sacrificed 3 days after exposure. The mice were exposed to PERC concentrations of 200, 400, 800, or 1600 ppm (1,356, 2,713, 5,426, or 10,852 mg/m^3) for 4 hours. Tissues were studied microscopically to assess the extent of necrosis and that of fat infiltation of the liver. Moderate to massive infiltration was observed in mice killed 1 or 3 days after exposure at 400 ppm (2,713 mg/m^3) or more, but no cell necrosis was observed even after 4 hours exposure up to 1600 ppm (10,852 mg/m^3) PERC.

Exposure to 200 ppm (1,356 mg/m^3) for 4 hours daily, 6 days a week, for up to 8 weeks was found to increase the severity of the lesions caused by PERC. Kylin et al. (1963) exposed four groups of 20 albino mice to 200 ppm (1,356 mg/m^3) PERC. Each group was exposed for 4 hours per day, 6 days/week, for 1, 2, 4, or 8 weeks. Microscopic examinations were performed on livers and kidneys of the exposed mice and controls. Fatty degeneration was particularly marked and tended to be more severe with longer exposure to PERC. Chemical determination of the liver fat content was performed in addition to the histologic examination. Correlation between the histologically evaluated degree of fatty degeneration and the concentration of extracted fat was +0.74. Liver fat content of the exposed animals was between 4 and 5 mg/g body weight as compared to 2 to 2.5 mg/g for the control animals. The actual fat content of the livers did not increase with duration of exposure as did the extent of the fatty infiltration. No liver cell necrosis was observed. No effect on the kidneys was reported.

Mazza (1972) exposed 15 male rabbits, 4 hours per day, 5 days a week, for 45 days to 2,790 ppm (18,924 mg/m^3) PERC. He looked at the effect of PERC on serum enzyme levels in an attempt to determine the specific location of initial liver injury as well as the severity of the damage to the liver. The Schmidt Index, which is the sum of SGOT and the SGPT divided by the serum glutamate dehydrogenase (GDH), was used as an indication of hepatic disorders. Enzymatic determinations were made before exposure and 15, 30, and 45 days after exposure to PERC. All three of the enzymes showed an increase in activity, but the GDH increased the most, reducing the Schmidt Index from 6.70 to 1.79. Mazza concluded that this reduction indicates the prevalence of mitochondrial injury over cytoplasmic injury in the liver.

Mazza and Brancaccio (1971) exposed 10 rabbits for 4 hours per day, 5 days per week, for 45 days to 2,790 ppm (18,924 mg/m^3) PERC. These investigators found a moderate, but not statistically significant, increase in levels of adrenal cortical and medullar hormones--plasma and urinary corticosteroids and catecholamines--including increased excretion of 3-methoxy-1-hydroxymandelic acid, the principal catecholamine metabolite.

In another study, Brancaccio et al. (1971) exposed 12 male rabbits for 4 hours per day, 6 days per week, for 45 days to 2,280 ppm (15,465 mg/m^3) PERC to look at effects on kidney function. They noted a reduction in glomerular filtration and renal plasma flow, and a decrease in the maximum tubular excretion when measured upon cessation of the exposure regimen. They concluded that PERC causes kidney damage, primarily in the renal tubule. These findings were in agreement with earlier histological findings of Pennarola and Brancaccio (1968) in which kidney injury, following exposure to PERC, appeared to be primarily in the renal tubule.

Plaa and Larson (1965) dosed mice with PERC by i.p. injection. Ten mice received 2.5 mg/kg and 10 others received 5.0 mg/kg. Urine samples were collected from surviving mice 24 hours after the injection of PERC. Protein was found in the urine of 1 of the 6 surviving mice injected with the lower dose and in 2 of 4 survivors of the higher dose at levels of 100 or more mg percent. None of the survivors had greater than 150 mg percent glucose in the urine. The kidneys of the mice given the lower dose were examined microscopically. The proximal convoluted tubules were swollen in all animals and necrotic in one.

Fujii (1975) observed an increase in serum enzyme activities (i.e., alkaline phosphatase, SGOT, and SGPT) within 24 hours after a single dose of 13 mmolePERC/kg given orally to rabbits. These changes in serum enzyme activities, indicative of liver damage, were mild and transient but followed a pattern similar to that seen with carbon tetrachloride.

6.2.3 Effects on the Heart

The possible cardiovascular effects of PERC have not been systematically investigated. Reinhardt et al. (1973) noted that PERC does not appear to sensitize the myocardium to epinephrine. In this study of dogs, a response considered indicative of cardiac sensitization was the development of a seriously life-threatening arrhythmia or cardiac arrest following a challenge dose of epinephrine. Tetrachloroethylene inhalation exposure for 10 minutes at concentrations of 5,000 or 10,000 ppm (33,915 or 67,830 mg/m^3) did not result in a positive response in any of the 17 dogs.

In the same study, sensitization did occur with the PERC analog, trichloroethylene, as well as with 1,1,1-trichloroethane, and trichlorotrifluoroethane. The investigators noted the possibility that PERC has the potential for cardiac sensitization, but to a lesser degree than the other chlorinated hydrocarbons studied.

Christensen and Lynch (1933) observed depression of the heart and respiration in five dogs, each given a single oral dose ranging from 4 to 5.3 ml/kg PERC. Autopsy showed fatty infiltration of both heart and liver tissue. The small intestine was extremely shriveled and showed marked inflammation.

6.2.4 Skin and Eye

Duprat et al. (1976) have shown PERC to be a primary eye and skin irritant in rabbits. Instillation of the chemical into the eye produced conjunctivitis with epithelial abrasion. However, healing of the ocular mucosa was complete within 2 weeks. Tetrachloroethylene had a severe irritant effect when a single application was made to the skin of the rabbit.

6.2.5 Other Effects Reported in Animals

Other effects which have been associated with exposure to PERC include changes in the immune system. Long-term inhalation exposure to PERC has been shown to cause distinct changes in immunological response in rabbits (Schmuter, 1972). Upon exposure of an unspecified number of rabbits to 15 and 1.5 ppm (102 and 10.2 mg/m^3), titers of typhoid antibodies were reported to have decreased.

Tarasova (1975) described the action of PERC on mast cells. Morphology of cells from albino rats exposed to 184 ppm (1,250 mg/m^3) was more varied. Cells appeared swollen. Vacuolization of the cytoplasm and conglomeration of granules was noted as well as increased degranulation.

Tsulaya et al. (1977) exposed 15 albino male rats continuously for 94 days to 0.6 and 2.8 ppm (4.2 and 19.3 mg/m^3) PERC. In the high exposure group, intensification of desquamative-proliferative processes in the bronchial and bronchiolar epithelium was observed, in addition to reactive changes in the mesothelium of pleura. An increase in the activity of succinic dehydrogenase in the epithelium of the lobes of the lungs was reported for both exposure groups. Histomorphological changes in lungs of low exposure group were not evident. Degranulation of mast cells was elevated over that observed in controls, only in the high exposure group.

Effects of PERC and other chlorinated and nonhalogenated hydrocarbons upon the lungs of rats were also investigated by Bonashevskaya (1977b). An unspecified number of rats was exposed continuously for 3 months, to levels of 0.7 and 2.7 ppm (4.5 and 19 mg/m^3). In the low exposure group, succinic dehydrogenase, lactic dehydrogenase, and glucose-6-phosphate dehydrogenase activities of the lung were elevated. In the high exposure group, cilia of the epithelium, in places, were detached or appeared agglutinated. The presence of acidic mucopolysaccharides was reported. The number of macrophages was elevated in the interalveolar septa, lumen of the bronchioles and alveoli. The activities of NAD and NADP-diaphorase in mesothelial cells of the pleura were elevated.

Rats fed a high protein diet (18 gm%) appeared to be more resistant to the effects of subcutaneous injection (0.4 ml daily, for 8 weeks) of PERC than rats fed a protein deficient diet (9 gm %) (Dumitrache et al., 1975). At low protein levels, red blood cell and hemoglobin levels were diminished as compared to initial levels. In addition, PERC treatment was statistically correlated ($p < 0.001$) with an increase in total serum lipids, with serum triglycerides ($p < 0.05$), and with a reduction in serum phospholipids ($p < 0.003$). Effects upon the liver were described previously.

Treatment of rats with a single i.p. dose of 1.3 ml/kg PERC alters the excretory function of the common bile duct and pancreas. (Harms et al., 1976) Hamada and Peterson (1977) demonstrated that the mechanism by which PERC increases "bile duct pancreatic fluid" flow does not appear to involve secretin or cholinergic stimulation.

Therapeutic doses of PERC in dogs have been shown to have effects on the heart, liver, and small intestine (Christensen and Lynch, 1933). Five dogs were starved for 24 hours prior to administration (1 to 3 cc) of PERC. A magnesium sulfate purge was administered 4 hours after dosage. After sacrifice, liver exhibited fatty infiltration and the small intestine was markedly inflamed. PERC had been administered as single doses and repeated doses. In all cases, PERC was reported to have caused considerable depression of the heart and of respiration. Repeated dosing caused more severe damage to liver and heart than single doses. No adverse effects upon kidney tissue were noted after any dosing reqime.

6.3 ADVERSE EFFECTS OF SECONDARY POLLUTANTS

Phosgene, a respiratory toxicant, is believed to originate via photodegradation of PERC and trichloroethylene in ambient air (Singh, 1976). Singh (1976) measured a mean value of 31.7 ppb during a 24-hour measuring period in urban Los Angeles.

Due to the lack of definitive data on the long-term effects of phosgene on humans, the National Institute for Occupational Safety and Health (NIOSH,

1976) recommended that the Occupational Safety and Health Administration federal standard of 0.1 ppm be maintained, to protect workers from long-time effects.

In acute overexposure situations, the concentrations had been generally unknown. The spectrum of effects have been described as acute bronchitis (Glass et al., 1971) to pulmonary edema and death (Spolyar, et al., 1951). Similar effects have been noted during experimentation on animals (Gross et al., 1965; Rinehart and Hatch, 1964).

In his review of the medical problems caused by phosgene, Diller (1978) stated that immediate and irreversible damage occurs when phosgene reaches the alveolar region of the lungs; membrane function breaks down and fluid leaks from the interstitial space into the alveolar space. For phosgene, the average lethal exposure dose (LCT50) in man is approximately 500 ppm/min (Moeschlin, 1965). Diller (1978) defined a serious exposure in which the dose is greater than 50 ppm/min.

In order to elucidate the effects of phosgene upon the lung, Forsolono and Pawlowski (1977) exposed male CFE Carworth rats to 1,000 and 2,400 ppm phosgene/min and determined the degree of pulmonary edema and lung enzyme levels in isolated lungs. Exposures were for 10 minutes. The LCT50 for rats is estimated at 1,625 and 350 ppm-min for 1- and 30-minute exposure periods, respectively. Phosgene was observed to inhibit the activities of cytochrome c oxidase, adenosine triphosphatase, and lysosomal activity. A marked increase in serum lactic dehydrogenase, often associated with pulmonary infarcts, was observed. In a separate experiment in which the phosgene dose was within or exceeded the LCT50, the investigators noted that the first ultrastructural alteration of vesiculation of cells in the terminal bronchiolar epithelium and most probably represented the beginning of edema.

Phosgene also is suspected of involvement in hepatotoxicity since it has been observed to be formed during metabolism of chloroform (Mansuy et al., 1977; Pohl et al., 1977; Cresteil et al., 1979).

Cresteil et al., in in vitro experiments with liver microsomes from rats, observed that production of endogenous phosgene is dependent upon the nucleophiles present in the incubation medium. Among potential metabolic products of phosgene are carbon dioxide, 4-carboxy-thiazolidene-2-one (reaction product of cysteine with phosgene), or unstable acyl chlorides. The authors stated that chloroform hepatotoxicity also involves phosgene since human microsomes behaved similarly as rat microsomes.

Although the level of phosgene derived from photodecomposition of PERC is not likely to result in serious long-term effects, these levels may present an added burden when one considers exposure in occupational settings or under certain conditions in which phosgene is directly formed from halocarbons, at high temperatures (e.g., cigarette smoke, welding).

6.4 SUMMARY OF ADVERSE HEALTH EFFECTS AND ASSOCIATED LOWEST OBSERVABLE EFFECT LEVELS

6.4.1 Inhalation Exposure

A number of case reports are available which describe accidental or occupational exposure to PERC. The duration and extent of exposure, however, either were unknown or involved excessively high concentrations. The few controlled human studies available generally provide information on effects resulting from short-term exposures at levels near 100 ppm (678 mg/m^3). Effects associated with chronic exposures, on the other hand, are available from animal experiments.

6.4.1.1 Effects Associated With Intermittent Or Prolonged Exposure--The data available from both human and animal exposures to PERC indicate that the CNS, liver, and kidneys are adversely affected. In the only controlled study involving humans, Stewart and coworkers (1977) exposed 12 individuals to 25 and 100 ppm (170 and 678 mg/m^3), 5.5 hours/day, for 3 months (55 exposures). There was a detrimental effect upon coordination, as measured by the Flanagan test, but no alterations in the EEG patterns, at 100 ppm (678 mg/m^3); there were no observed effects at 25 ppm (170 mg/m^3).

The data summarized in Table 6.1 indicate that prolonged exposure may cause liver and kidney damage, as indicated by abnormal liver and kidney function parameters. In several instances, elevated liver function parameters were observed during the postexposure period, suggesting that the liver may be subject to a continuing insult as a result of slow release from tissues.

Both subchronic and chronic inhalation exposures of animals support the observations in humans. Carpenter (1937) observed dose-related congestion and swelling in the livers and kidneys of rats exposed for 8 hours/day, 5 days per week, for 7 months, to 230 and 470 ppm (1,559 and 3,187 mg/m^3) PERC. Rowe et al. (1952) observed degenerative changes in the livers of guinea pigs, a species that appears more sensitive to PERC, following an 8-month exposure to 200 and 400 ppm (1,356 and 2,712 mg/m^3), for 7 hours per day, 5 days per week.

Carpenter (1937) reported[a] no observable effects level (NOEL) at 70 ppm (475 mg/m^3) in rats exposed 8 hours per day, 5 days per week, for 7 months. A histologic examination of the liver, kidneys, spleen, heart, brain, eye, and nerve tissue, as well as blood and urine analyses, were performed. The NOEL is defined as that exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and the appropriate control. In contrast to the absence of effect of exposure of humans to 25 ppm (170 mg/m^3) on EEG patterns, four reports in the Russian literature indicate the chronic exposure of rats and rabbits produced abnormal EEG patterns at 15 ppm (102 mg/m^3). Animals were exposed from 7 to 11 months, for 3 to 4 hours/day, 6 to 7 days per week. Depressed agglutinin formation also was reported. Because these reports lacked adequate description of experimental design and results, it is difficult to evaluate these data until replicated by other investigators. The apparent discrepancy between the observations of Stewart et al. (1977) and the Russian investigators may be related to exposure duration and/or differences in experimental procedure, rather than indicating a greater sensitivity of rats than humans to PERC.

The available evidence suggests that a prolonged exposure level of about 100 ppm (678 mg/m^3) represents the lowest-observed-adverse-effect level, (LOAEL) in humans. It should be noted that prolonged exposure at or near this concentration may not protect all individuals from slight liver and kidney damage. The LOAEL is defined as the lowest exposure level in a study or group of studies which produces statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

6.4.1.2 Effects Associated With Short-term Exposure--Controlled studies in humans have provided information on a progression of effects upon the CNS, ranging from lightheadedness to narcosis, and subsequently death. A summary of the estimated dose-response relationships for acute effects of single, short-term exposures of humans is presented below:

> 4,000 ppm	possibly life-threatening
2,000 ppm	light narcosis, possible liver damage
1,000 ppm	lightheadedness
200 ppm	possible reversible fatty changes in the liver
100 ppm	first signs of CNS depression, giddiness, slight eye irritation
75 ppm	very slight eye irritation
5 ppm	odor threshold

Stewart et al. (1970) reported lightheadedness in 25 percent of the 15 volunteers exposed for 7 hours to an average PERC concentration of 101 ppm

(685 mg/m^3). Rowe et al. (1952) reported lightheadedness in four individuals exposed for 2 hours to 216 ppm (1,465 mg/m^3), but not in six individuals exposed 2 hours to 106 ppm (719 mg/m^3). The observations in these studies follow the expected pattern for a non-specific anesthetic effect. It can be concluded that a short-term exposure to about 100 ppm (678 mg/m^3) will result in some individuals experiencing the first gross signs of CNS depression and behavioral alterations. However, more sensitive tests of CNS involvement such as tests of coordination, may reveal that PERC has adverse effects at even lower concentrations. There also are indications that short-term exposures may damage the liver. Kylin et al. (1963) reported transient moderate fatty infiltration in livers of mice exposed for 4 hours to 200 ppm (1,356 mg/m^3). Liver damage in humans, however, is generally associated with short-term exposures greatly in excess of 100 ppm (678 mg/m^3).

6.4.2 Oral Exposure

As summarized in Table 6-2, the acute oral toxicity of PERC has been determined in rats, mice, cats, rabbits, and dogs. The LD_{50} values in rats and mice were 4,000 and 8,000 mg/kg, respectively. There are no subchronic oral exposure studies and only one chronic study, the NCI bioassay. Neither of these studies identifies either a NOEL or LOAEL.

6.4.3 Dermal Exposure

Although PERC can be absorbed through unbroken skin, absorption was estimated to be minor (Stewart and Dodd, 1964). It is unlikely that toxic quantities would be absorbed through this route.

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7. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

As for any highly lipid soluble chemical that readily crosses the human placental barrier into the fetus (Helliwell and Hutton, 1950; Lanham, 1970), perchloroethylene (PERC) warrents consideration as a potential teratogen.

In particular PERC may pose a human teratogenic hazard because of its widespread use and its potential for retention in lipid-rich tissues. Also, PERC is preferentially concentrated in maternal milk and this makes it a chemical of particular hazard to neonates (Bagnell and Ellenberger, 1977). A discussion of the effect of PERC-contaminated mother's milk is discussed in Chapter 6.

7.1 ANIMAL STUDIES

It is not possible, on the basis of limited available data, to define the full potential of PERC to produce adverse teratogenic or reproductive effects. The available mammalian studies were not properly designed to evaluate the ability of PERC to produce a teratogenic response over a wide range of doses which include doses high enough to produce signs of maternal toxicity and lower doses which do not produce maternal toxicity. The teratology studies in laboratory animals were performed in rats, mice, and rabbits using only single doses of PERC which produced signs of maternal toxicity. Other studies in chicken embryo have indicated that PERC disrupts embryogenesis in a dose-related manner; however, since administration of PERC directly into the air space of chicken embryo is not comparable to administration of dose to animals with a placenta, it is not possible to interpret this result in relationship to the potential of PERC to cause adverse human reproductive effects. Another preliminary study in rats indicated that adverse behavioral effects may occur after exposure to low levels of PERC. However, additional behavioral studies, using larger number of animals for statistical evaluation have not been conducted to more fully evaluate this effect. It should also be noted that no multi-generation reproductive study has been conducted. In summary, although several studies have been conducted to evaluate PERC to cause adverse teratogenic, embryotoxic and reproductive effects, the limitations of the available data does not allow for a full assessment of these effects. A better assessment of these effects could be performed if the available animal studies met criteria similar to those suggested for teratogenicity and reproductive testing (U.S. EPA, 1978, 1979). The following discussion of studies subscribes to the basic viewpoints and definitions of the terms "teratogenic" and "fetotoxic" as summarized and stated by Chernoff (1980):

> Generally, the term "teratogenic" is defined as the tendency to produce physical and/or functional defects in offspring in utero. The term "fetotoxic" has traditionally been used to describe a wide variety of embryonic and/or fetal divergences from the normal which cannot be classified as gross terata (birth defects) -- or which are of unknown or doubtful significance. Types of effects which fall under the very broad category of fetotoxic effects are death, reductions in fetal weight, enlarged renal pelvis edema, and increased incidence of supernumary ribs. It should be emphasized, however, that the phenomena of terata and fetal toxicity as currently defined are not separable into precise categories. Rather, the spectrum of adverse embryonic/fetal effects is continuous, and all deviations from the normal must be considered as examples of developmental toxicity. Gross morphological terata represent but one aspect of this spectrum, and while the significance of such structural changes is more readily evaluated, such effects are not necessarily more serious than certain effects which are ordinarily classified as fetotoxic--fetal death being the most obvious example.
>
> In view of the spectrum of effects at issue, the Agency suggests that it might be useful to consider developmental toxicity in terms of three basic subcategories. The first subcategory would be embryo or fetal lethality. This is, of course, an irreversible effect and may occur with or without the occurrence of gross terata. The second subcategory would be teratogenesis and would encompass those changes (structural and/or functional) which are induced prenatally, and which are irreversible. Teratogenesis includes structural defects apparent in the fetus, functional deficits which may become apparent only after birth, and any other long-term effects (such as carcinogenicity) which are attributable to in utero exposure. The third category would be embryo or fetal toxicity as comprised of those effects which are potentially reversible. This subcategory would therefore include such effects as weight reductions, reduction in the degree of skeletal ossification, and delays in organ maturation.

Two major problems with a definitional scheme of this nature must be pointed out, however. The first is that the reversiblity of any phenomenon is extremely difficult to prove. An organ such as the kidney, for example, may be delayed in development and then appear to "catch up". Unless a series of specific kidney function tests are performed on the neonate, however, no conclusion may be drawn concerning permanent organ function changes. This same uncertainty as to possible long-lasting after effects from developmental deviations is true for all examples of fetotoxicity. The second problem is that the reversible nature of an embryonic/ fetal effect in one species might, under a given agent, react in another species in a more serious and irreversible manner.

7.1.1 Chicken Embryos

The Elovaara et al. (1979) study reported relative toxicity and teratogenic potential of PERC in comparison with other aliphatic chlorinated hydrocarbons. The approximate LD50 of PERC was greater than 100 µmole/egg. Macroscopic embryonic malformations of various kinds were produced with doses of 5 to 100 µmoles/egg injected into the air space of fertilized chicken eggs at 2, 3, and 6 days of incubation. Embryotoxicity was evaluated as survival and death incidences after 14 days of incubation.

Malformations were observed in 6/61 (9.8 percent) embryos exposed to PERC, as compared with 2/56 (3.5 percent) control embryos exposed to olive oil. Exteriorization of viscera occurred in one PERC-exposed embryo; none occurred in the olive oil controls. Skeletal abnormalities occurred in five of the PERC-exposed embryos and in only one of the controls.

This type of study should be considered as a prescreen. Although the technique may be appropriate for comparative screening purposes (Johnson, 1981), it is not appropriate for determining teratogenic potential in mammals or man (Karnofsky, 1965).

7.1.2 Mice

Leong et al. (1975) and Schwetz et al. (1975) reported a study of Swiss-Webster mice exposed to PERC via inhalation at concentrations of 300 ppm for 7 hours daily on days 6 through 15 of presumed gestation. Day 0 of gestation was designated the day a vaginal plug was observed. This concentration was cited as twice the maximum allowable excursion limit for human industrial exposure, with the threshold limit value as 100 ppm (678 mg/m^3). Concurrent controls were exposed to filtered air.

Following maternal Caesarean-sectioning on day 18 of gestation, all fetuses were examined for external anomalies. One-half of the fetuses were examined for soft tissue malformations using a free-hand sectioning technique, and the other one-half of the fetuses were cleared, stained, and examined for skeletal malformations. One fetus in each litter was processed and examined using histopathological techniques. A total of seventeen litters were examined. The pups in the exposed group were signficantly smaller as measured by decreases in fetal body weight. Also slight, but not statistically significant, increases in the number of runts, were observed, as well as fetuses with subcutaneous edema, delayed ossification of the skull, delayed ossification of the sternebrae and splits in sternebrae. No other remarkable malformations were reported in fetuses. Increases in the absolute and relative mean maternal liver weights were reported.

7.1.3 Rats

Leong et al. (1975) and Schwetz et al. (1975) reported a teratology study in Sprague-Dawley rats. The compound was administered by inhalation, 300 ppm (2,034 mg/m^3) for 7 hours daily, on days 6 to 15 of gestation. Control rats were exposed to filtered air. Day 0 of gestation was designated as the day when spermatozoa were observed in smears of vaginal contents. Rats were sacrificed on day 21 of gestation, Caesarean section performed, and fetuses examined for external malformations. One-half of the fetuses in each litter was examined for soft tissue malformations and the remaining one-half of the fetuses were examined for skeletal malformations. One fetus from each litter was randomly selected for serial sectioning and histological evaluation.

Average maternal body weight gain was slightly reduced in the rats exposed to PERC. A statistically significant increase in resorption was reported in 17 PERC-exposed litters evaluated. Exposure of dams to PERC produced no effect on the average number of implantations per litter, fetal sex ratios, or fetal body measurements. No soft tissue or skeletal anomalies were reported in the offspring of rats exposed to PERC.

Beliles et al. (1980) reported another study using Sprague-Dawley rats. Tetrachloroethylene, 300 ppm (2,034 mg/m^3), was administered via inhalation to rats for 7 hours daily, 5 days per week. Controls were administered filtered air. One-half of the rats were exposed for 3 weeks prior to mating. All rats were exposed during gestation on either days 0 through 18, or days 6 through 18, with day 0 designated as the day when spermatozoa were observed in smears of vaginal contents. It should be noted that the information in the report indicated that a Monday through Friday treatment period was used. If the exposure during the gestation period is correctly reported, rats supposedly exposed on days 0 through 18 would not have been administered PERC on days 5, 6, 12, and 13. Similarly, in rats supposedly treated on days 6 through 18 exposure would not have been exposed on days 11, 12, and 18. Thus, questions arise as to whether the treatment intervals cited were actually the ones performed. Unless all rats were mated on a single day, or unless treatment was available on a 7 day/week basis, the rats may not have been exposed on the days cited. This point needs to be clarified with the investigators.

In this study, 3 rats died following exposure of 568 ppm (3,390 mg/m^3) PERC during the last 2 hours of the second day of pregestational treatment. Ataxia was observed in the other rats of this dosage group. The maternal body weight gain in the PERC-treated rats was not statistically different from controls during the pregestational period. Inhibition of maternal body weight gain occurred during the first week, as well as increases in mean absolute, but not relative kidney and liver weights. No embryotoxic effects were observed which were attributable to maternal exposure to PERC except for delays in skeletal ossification. This effect, however, is thought to be a reversible effect and not considered a malformation as such. However, it should be noted that inadequacies in this study such as the fact there was only one dosage level used, prevent firm conclusions to be made on the potential of PERC to cause adverse effects on the developing conceptus.

Nelson et al. (1980) evaluated the ability of PERC to elicit a behavioral teratogenic response in Sprague-Dawley rats. It should be noted that very small numbers of animals were used in this study. In a pilot study rats were exposed to the 900 ppm (6,102 mg/m^3) PERC on days 7 to 13 of gestation, and signs of maternal toxicity such as severe depressions in average food intake, and decreased average body weight gain, were observed. Food consumption and body weight gain were also reduced but not statistically so, in rats exposed to 900 ppm (6,102 mg/m^3) PERC on days 14 to 20 of gestation. Dams and pups exposed to 100 ppm PERC (678 mg/m^3), on days 14 to 20 of gestation, did not show any adverse effects as compared to the controls.

In the same study, narcotization occurred in groups of 3 animals exposed to 3,600 or 1,800 ppm (24,408 or 12,204 mg/m^3) PERC. There is some question as to whether the rats exposed to 3,600 ppm (24,408 mg/m^3) died since no mention was made of the group treated with 3,600 ppm PERC (24,408 mg/m^3), the report stated only that "In the small number of mothers which survived exposure to 1,800 ppm (24,408 mg/m^3) PERC, there was a small increase in resorptions, but no malformations were detected." Pups observed in weeks 3, 4, and 5 from dams exposed to 900 ppm (6,102 mg/m^3) PERC on days 14 to 20 of gestation had a reduction in body weights of approximately 20 percent.

In the behavioral testing study, 102 pregnant rats were randomly assigned to the following groups:

(1) 900 ppm PERC, days 7-13 (N = 19)	(4) sham exposed, days 14-20 (N = 19)
(2) 900 ppm PERC, days 14-20 (N = 21)	(5) 100 ppm PERC, days 14-20 (N = 15)
(3) sham exposed, days 7-13 (N = 13)	(6) sham exposed, days 14-20 (N = 15)

Seven behavioral tests were performed on days 4 through 46 postparturition, using only one male and one female rat per litter. Olfaction was tested on three groups of rats per litter. One pair of rats were tested for ascent on a wire mesh screen and rotorod balancing. Another pair of rats were tested for open-field activity, activity wheel, and avoidance condition. The third pairs of rats were tested for operant conditioning. Catecholamines (norepinephrine and dopamine), acetylcholine, and protein measured in the brain tissue were evaluated in ten pups (no more than two per litter) at birth, and at 21 days postparturition. Histopathological evaluation of brains for neuropathology was performed in an unreported number of pups.

Rats exposed to 900 ppm PERC on days 7 to 13 of gestation, performed less well on discrete testing of ascent and rotorod tests. Offspring exposed to 900 ppm (6,102 mg/m^3) on days 14 to 20 of gestation performed less well in the ascent test, but later performed better than controls in the rotorod test, and were relatively more active than controls in the open-field tests. Acetylcholine levels were reduced in 21-day-old rats exposed to 900 ppm (6,102 mg/m^3) PERC. Dopamine levels were reduced in rats exposed to PERC on days 7 to 13 of gestation.

The changes observed in this study on behavioral teratogenic effects cannot be interpreted in terms of human risk assessment resulting from low level exposure of PERC at this time. This is because alterations in maternal nutritional status have been known to produce "CNS-behavioral" alterations (Dobbing et al., 1971) and that the entire field of behavioral teratology is in its early stages of development (Buel ke-Sam and Kimmel, 1979) and behavioral alterations cannot be interpreted in terms of human effect.

7.1.4 Rabbits

Beliles et al. (1980) administered 500 ppm PERC, via inhalation, to rabbits for 7 hours/day, 5 days/week. One-half of the rabbits were exposed for 3 weeks prior to and during gestation, the other half were exposed during gestation only. During gestation, rabbits were exposed to 500 ppm for 7 hours/day, 5 days/week, on days 0 through 21, or days 6 through 21. Control rabbits were exposed to filtered air. Day 0 of gestation was defined as the day natural mating was observed. Rabbits were Caesarean sectioned on day 30 of gestation. Maternal body weights, food consumption, and organ weights were reported. All fetuses were examined for soft tissue and skeletal malformations.

Decreases in food consumption were observed in rabbits exposed to PERC during gestation only, and increases in food consumption were observed after the treatment period in rabbits exposed both before and during gestation. Delays in fetal ossification were observed in exposed groups.

As in the studies by the same authors, Beliles et al. (1980), in rats there are questions as to whether exposures occurred as the regime stated or if there were problems with treatments only on a Monday through Friday basis. Again this question about dosage regime should be clarified with the authors.

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8. MUTAGENICITY

Tetrachloroethylene has not been clearly demonstrated to cause point mutations in bacteria. It should be noted, however, that negative results in bacteria does not preclude mutagenic activity in another organism. There is suggestive information that PERC may be genetically active in yeast. Discussion of the mutagenicity of PERC is provided in the Appendix.

Additional studies are required to further evaluate the mutagenic potential of PERC.

9. CARCINOGENICITY

The intent of this chapter is to summarize the scientific evidence relating to the carcinogenic potential of PERC. For an in-depth discussion of the findings in each of the studies cited, the reader is referred to the report of the U.S. E.P.A. Carcinogen Assessment Group that is appended to this document.

9.1 ANIMAL BIOASSAYS

9.1.1 National Cancer Institute (NCI) Bioassay

Tetrachloroethylene was one of several halogenated hydrocarbon compounds selected for bioassay. Among the reasons for its selection was (1) a lack of adequate toxicity data, (2) its chemical structure (3) high production volume, and (4) extensive use (NCI, 1977; Weisburger, 1977).

Tetrachloroethylene was administered, in a corn oil vehicle by gastric intubation, to male and female Osborne-Mendel rats and to male and female B6C3F1 mice. It was administered at two dose levels, 5 days per week, for 78 weeks. The compound induced a statistically significant ($p<0.001$) increase in the incidence of hepatocellular carcinomas, at both dose levels in both sexes of mice. No carcinogenic effect was observed in lifetime studies of Osborne-Mendel rats. However, because of excessive dose-related mortality no conclusions can be drawn. A gavage study in four rat strains, now in progress at NTP, should clarify the nature of the rat response.

It should be noted that the purity of the test material used in the NCI study was at least 99 percent PERC. However, it was estimated that the test mixture contained an epichlorohydrin concentration of less than 500 ppm. While it is unlikely that the response in these rodents could be attributed to this epichlorohydrin concentration, the NCI is testing this possibility in a bioassay now in progress. In the ongoing bioassay, epichlorohydrin-free PERC is being administered via gavage to B6C3F1 mice.

The incidence of nonneoplastic lesions of the liver in both male and female mice from the NCI study (1977) were reviewed. This study did not reveal statistically significant nonneoplastic lesions which could be correlated with neoplastic lesions of the liver.

9.1.2 Dow Chemical Company Rat Inhalation Study

In this study by Rampy et al. (1978), two groups of Weanling Sprague-Dawley (Spartan substrain) rats, 96 males and 96 females each, were exposed to 600 ppm (4.07 mg/l air) or 300 ppm (2.03 mg/l air) PERC for 6 hours per day, 5 days per week, for 52 weeks. A carcinogenic response was not observed, as judged from pathologic examination of the animals. Although many tumor types were found in treated and control animals, there was no statistically significant ($p<0.05$) increase in tumor incidence at any anatomical site.

9.1.3 Intraperitoneal Studies

Thiess et al. (1977) tested PERC for a carcinogenic response in the strain A mouse pulmonary tumor induction system. The test sample was reported to be reagent grade with a purity in the range of 95 to 99 percent. The maximum tolerated dose to five Strain A/St male mice was determined over a 2-week injection period, followed by a 4-week observation period. In the bioassay 20 mice per treatment group received three injections of PERC weekly until total dosages of 1,120; 4,800 and 9,600 mg/kg were achieved. Administration of PERC did not statistically increase ($p<0.05$) the incidence of pulmonary tumors.

It was noted by the investigators that the strain A mouse pulmonary tumor assay is relatively insensitive to mouse carcinogens for which the effect is confined to the liver. The negative result in this assay is not considered conclusive since several chemicals known to be carcinogenic in chronic rodent bioassays induce no response in this assay. The reasons for the negative lung response are not understood but may be due to a smaller concentration of activating enzymes in the lung than in the liver.

9.1.4 Skin Painting Studies

A study using purified PERC on ICR/Ha Swiss mice was described by Van Duuren et al. (1979). Maximum tolerated doses were determined in range-finding studies, 6 to 8 weeks in duration. Doses selected were those that did not affect body weight gain nor produce clinical signs of toxicity.

Female mice were treated topically on dorsal skin with a simple application of 163 mg PERC, followed 14 days later by applications of 5.0 µg phorbol myristate acetate to the skin, three times weekly until termination of the study at 428 to 576 days. The vehicle, acetone, was applied to a control group of 30 mice. A group of 100 mice served as untreated controls.

Tetrachloroethylene did not show initiating activity in the initiation-promotion experiment. The negative results with mouse skin as an initiator and as a complete carcinogen can be reconciled with the positive mouse liver response in the NCI bioassay if it is hypothesized that the skin does not have the necessary enzymes to convert PERC to an active metabolite.

9.2 EPIDEMIOLOGICAL STUDIES

9.2.1 National Institute for Occupational Safety and Health (NIOSH) Study

This investigation is a retrospective cohort study of mortality of dry cleaning workers exposed to PERC for at least one year prior to 1960. Kaplan (1980) reported that efforts were made to exclude all persons with previous occupational exposure to carbon tetrachloride or trichloroethylene. The study cohort, selected from records maintained by several labor unions, consisted of 1,597 individuals employed more than one year prior to 1960 in dry cleaning establishments.

As detailed in the Carcinogen Assessment Group report, no conclusions can be drawn from the study because of deficiencies in study design and interpretation.

9.2.2 National Cancer Institute (NCI) Study

In this proportionate mortality study of laundry and dry cleaning workers who had been exposed to various solvents, Blair et al. (1979) reported an increased risk for malignant neoplasms. As detailed in the Carcinogen Assessment Group report, this finding should be regarded as only suggestive of a carcinogenic effect because of the limitations of the proportionate mortality approach and because the deaths included in the study constitute only a nonrandom and possibly biased subset of total deaths among individuals even belonging to the two locals under study.

9.2.3 Oklahoma Dry Cleaning Workers

In this ongoing study of death certificates of dry cleaning workers in Oklahoma, preliminary results suggest increased death from kidney cancer in male workers (Assad, 1980). Details of the study are not yet available to assess its significance.

9.2.4 Other Studies

Two retrospective studies have been performed recently using hospital medical records and death certificates for people employed in the dry cleaning and laundry industries. In the study by Lin and Kessler (1981), medical records obtained from 115 hospitals were used to identify both individuals who had a specific type of cancer and a group of cancer-free matched controls. One of the associations observed was a relationship between pancreatic cancer and exposure to dry cleaning chemicals and gasoline fumes. Although this relationship suggests the need for further epidemiological studies that focus on the hazards of the dry cleaning industry, the lack of information on the extent or type of chemical exposure does not allow an association to be made between PERC exposure and pancreatic cancer. In the second study, Katz and Jowett (1981) examined the death certificates of 671 female workers in the laundry and dry cleaning industry in order to determine the cause of death. The cause-specific proportionate mortality ratios (PMRs) were calculated for 25 major causes of death, using female workers in the catagories of service and operative workers for comparison. An elevated risk of genital (unspecified) and kidney cancer was observed along with an elevated risk of Diabetes Mellitus. The authors speculated that PERC may be one of the causative agents, however, the lack of exposure data on the extent of exposure and the types of chemicals to which the workers were exposed makes this interpretation speculative. Both of these studies indicate that further evaluation is needed of possible effects of human exposure to PERC as encountered in the laundry and dry cleaning industries.

9.3 REFERENCES FOR CHAPTER 9

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10. SYNERGISMS AND/OR ANTAGONISMS

Little information is available concerning the synergistic and/or antagonistic potential of PERC.

Administration of diazepam (Valium®) or ethanol (in the form of 10 and 20 percent vodka in orange juice) to male and female volunteers combined with exposure to 25 or 100 ppm (170 or 678 mg/m^3) PERC did not exacerbate the behavioral and/or neurological effects noted with either alcohol or diazepam alone (Stewart et al., 1977). An inconsistent increase in the beta activity of the EEG during combined PERC exposure and diazepam dosing was noted. This effect was attributed to diazepam alone. Diagnostic tests administered included the Michigan eye-hand coordination test, Rotary Pursuit, Flanagan coordination test, Romberg test, Saccade eye velocity test, dual-attention tasks, and a mood evaluation test. Cornish and Adefuin, (1966) observed no potentiating action of prior ethanol ingestion on acute inhalation toxicity of PERC in rats. Phenobarbital pretreatment of rats also did not potentiate toxicity of PERC administered i.p. to rats (Cornish et al., 1973).

Smythe et al. (1969) observed that PERC, when administered in an oral dosing regimen with other compounds, produced a greater-than-additive response. PERC was administered to female albino rats in a 50:50 mixture with each of 26 industrial chemicals. LD_{50}'s were determined and compared to a predictive LD_{50} determined according to the procedure of Finney (1952). Those mixture which deviated most (more than two standard deviation units) from predicted values included PERC in combination with each of the following chemicals: butyl ether, polyethylene glycol 400, and acetophenone.

Withey and Hall (1975) exposed rats to mixtures of PERC and either benzene or toluene. PERC in combination with benzene yielded LD_{50} values that were slightly less-than-additive; PERC and toluene yielded an LD_{50} that deviated from that predicted on the basis of additive effects.

Drew et al. (1978) evaluated changes in serum enzymes before and after rats were exposed by inhalation to PERC in combination with other compounds. Neither PERC in combination with dioxane, butyl ether, nor acetonitrile resulted in a greater-than-additive effects. PERC was administered at three nominal levels: 500, 1,000 and 2,000 ppm (3,390, 6,780, and 13,560 mg/m^3). Given alone, PERC was observed to result in marked elevations in SGOT, SGPT, glucose-6-phosphatase, and ornithine transcarbamylase.

Stewart et al. (1961) reported no neurological abnormalities during or 6 weeks after an accidental exposure to 393 ppm (2,666 mg/m^3) PERC and Stoddard solvent.

Clinical exposure of five individuals to a solvent mixture containing methyl chloroform (74 percent) and PERC (22 percent) did not reveal any deleterious neurological findings beyond which would be found upon exposure to each alone (Rowe et al. 1952). The exposure level of PERC was calculated at 100 ppm (678 mg/m^3). A complete examination was given at the end of the sixth hour of the 7-hour exposure period. Individuals were exposed for one, four, and five, 7-hour periods.

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11. REGULATIONS, STANDARDS, AND GUIDELINES

Emissions of tetrachloroethylene (PERC) are regulated on an individual state basis through the State Implementation Plans (SIPS). Most SIPS have used a modification of Rule 66 (now Rule 442), developed by the Los Angeles County Air Pollution Control District, in which emissions of photochemically-reactive solvents are limited to about 8 pounds per hour.

In the workplace, the current Standard of The Occupational Safety and Health Administration (OSHA) is 100 ppm (678 mg/m^3) over an 8-hour workday and 40-hour workweek. This standard allows a ceiling concentration of 200 ppm (1,356 mg/m^3) and a peak concentration of up to 300 ppm (2,034 mg/m^3) for any 5-minute timeframe, in any 3-hour period. Neither of these limits was based on findings other than toxicity. In the current bulletin of the National Institute for Occupational Safety and Health (NIOSH), it was recommended that PERC be treated in the workplace as if it were a human carcinogen. This interim recommendation was issued pending full evaluation of the carcinogenic potential of PERC.

The TLV®, expressed as a time-weighted average, is 100 ppm (678 mg/m^3); the health basis is chronic intoxication regarding the hepatic and CNS systems (Am. Conf. Gov. Ind. Hyg., Threshold Limit Values for Chemical Substances Physical Agents in the Workroom, Environment, 1979).

The U.S. Environmental Protection Agency has suggested ambient water quality criteria for PERC for the protection of human health and aquatic life. These criteria are based on scientific data and have no regulatory impact but may be useful in forming regulations (45 FR 79318-79319, 1980).

For the maximum protection of human health from potential carcinogenic effects due to exposure via contaminated water and contaminated aquatic organisms, ambient water concentrations would ideally have to be zero (Ambient Water Quality Criteria for Tetrachloroethylene, EPA 440/5-80-073, October 1980). Since the zero level is not attainable, the criterion recommended for ambient water quality was 0.80 μg/ℓ (at the 10^{-6} level of lifetime risk). The criteria was based upon a 70 kg adult unbibing 2 liters of water per day and the consumption of 6.5 grams of contaminated fish. Excluding water consumption and considering only the consumption of fish and shellfish, the recommended criterion becomes 8.85 μg/l. The criteria for protection of aquatic species are 5,280 and 840 μg/l, levels associated with the onset of acute and chronic toxicity to freshwater aquatic life. For saltwater aquatic life, acute and chronic toxicity occur at concentrations as low as 10,200 μg/l and 450 μg/l, respectively. Effects, however, may occur at lower concentrations among species that are more sensitive than those tested.

Levels judged to be protective of human health where drinking water is concerned are presently being formulated.

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EXTERNAL REVIEW DRAFT
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THE CARCINOGEN ASSESSMENT GROUP'S
CARCINOGEN ASSESSMENT
OF
TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

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This document has been reviewed and approved by the Chairman and staff of the Carcinogen Assessment Group, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency. It has not been formally released by the EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implication.

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I. SUMMARY AND CONCLUSIONS

QUALITATIVE ASSESSMENT

Three epidemiological studies on laundry and dry cleaning workers exposed to tetrachloroethylene are in progress, but only tentative conclusions can be drawn from them at this time. In one unpublished contractor report, the observation period was short, the extent of follow-up was incomplete, and important confounding variables were not assessed. A second report suggested a correlation between tetrachloroethylene exposure and lung, skin, and cervical plus uterine cancer, but the findings are still preliminary and are based on a proportionate mortality approach, which has inherent limitations. A verbal communication from the investigator of a third study suggests increased deaths from kidney cancer but the significance of this finding cannot be assessed until the study becomes available.

Tetrachloroethylene induced a statistically significant increase in the incidence of hepatocellular carcinomas at both high and low dose male and female B6C3F1 mice when administered by gavage for a period of 78 weeks. The tetrachloroethylene was over 99% pure but was estimated to contain epichlorohydrin concentrations of less than 500 ppm. It is unlikely that this response could be attributed to the low concentration of epichlorohydrin. Another study in this strain with purified tetrachloroethylene devoid of epichlorohydrin administered by gavage, now in progress at the National Toxicology Program (NTP), should clarify whether the response was due to an impurity.

No carcinogenic effect was observed in lifetime studies of Osborne-Mendel rats given the same product discussed above by gavage or in Sprague-Dawley rats via inhalation exposure for 12 months followed by 12 months observation. However, because of excessive dose-related mortality in the gavage experiment, and because of the low dose level in the inhalation study, no conclusions can be made about the carcinogenicity of tetrachloroethylene in rats. A gavage study in four rat strains, now in progress at NTP, should clarify the nature of the rat response.

Intraperitoneal injection of tetrachloroethylene in strain A mice induced no statistically significant incidence of pulmonary adenomas. In mouse skin initiation experiments, tetrachloroethylene did not initiate skin tumors, nor did it induce skin tumors when applied alone three times per week for the lifetime of the animals. The negative response in these assays does not detract from the positive findings in the National Cancer Institute (NCI) mouse experiment because of inherent limitations in these assays.

Information about the mutagenicity of tetrachloroethylene consists of six reports about bacterical systems, one yeast study, and two in vivo mammalian cytogenetic studies. Only one of the bacterial tests could be verified as positive and that was mutagenic only when the "stabilizer" was present along with tetrachloroethylene. Purified tetrachloroethylene produced no response in bacteria. The yeast test using thymol as a stabilizer was positive. The two mammalian cytogenic studies were negative, but could not be evaluated because of lack of detailed information about the assays. Tetrachloroethylene was found to transform rat embryo cells in culture according to one report.

Animal metabolism studies show that tetrachloroethylene is converted to tetrachloroethylene epoxide, which is a highly reactive compound. Epoxides as a group are regarded as having carcinogenic potential.

In summary, there is evidence that tetrachloroethylene is a potential human carcinogen, based on the definitive hepatocellular carcinoma response in both male and female mice and the metabolic evidence of a direct-acting epoxide metabolite. Applying the criteria for evaluation of experimental animal carcinogenicity studies used by the International Agency for Research on Cancer (IARC 1979), this level of evidence would be regarded as "limited," meaning not sufficient to provide a firm conclusion on its carcinogenic potential in humans. Two studies of laundry and dry cleaning workers have shown preliminary evidence of excess cancer incidence associated with tetrachloroethylene exposure, but no conclusion can be drawn from them until they are complete.

QUANTITATIVE ASSESSMENT

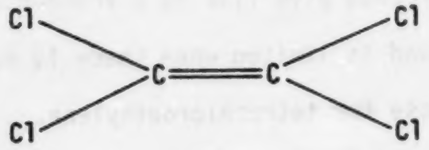
Upper-bounds of risk have been estimated for individuals undergoing either of two hypothetical lifetime exposure situations: 1) continuous exposure to 1 microgram of tetrachloroethylene per cubic meter of air, or 2) continuous exposure to 1 microgram per liter in drinking water. The estimate was based on the hepatocellular carcinoma response in male B6C3F1 mice given tetrachloroethylene by gavage for 78 weeks in the National Cancer Institute (NCI 1977) bioassay. The linearized multistage model is used for low-dose extrapolation in order to give an estimate of an upper-bound of lifetime cancer risk, recognizing that uncertainties in both the qualitative evaluation and the quantitative extrapolation process give risk to a lower-bound of zero risk. The plausibility of the upper-bound is limited when there is no direct evidence for genotoxicity, which is the case for tetrachloroethylene.

Using this procedure, the upper-bound of the individual lifetime cancer risk resulting from continuous exposure to air having tetrachloroethylene concentration of 1 ug/m^3 is 7.6×10^{-6}. The corresponding risk for a drinking water concentration of 1 ug/l is 3.6×10^{-7}. Because of the uncertainties in both the qualitative and quantitative aspects of risk assessment, the actual cancer risks may be lower than those indicated above, which should be regarded as plausible upper-limits and may approach zero.

II. INTRODUCTION

Tetrachloroethylene (perchloroethylene) is a colorless heavy liquid with a molecular weight of 165.85. It has a molecular structure ($Cl_2C=CCl_2$) closely related to trichloroethylene ($ClCH=CCl_2$), vinylidene chloride ($CH_2=CCl_2$), and vinyl chloride ($CH_2=CHCl$). Physical properties include a solubility in water of 150 mg/l at 25°C, ready solubility in organic solvents, a boiling point of 121°C, a specific gravity of 1.62, and a vapor pressure of 19 mm Hg at 26°C. Annual domestic production of tetrachloroethylene is approximately 300,000 metric tons. Its major uses are in the dry cleaning of fabrics and in the degreasing of metals. A recent draft report by Marra et al. (1979) of Stanford Research Institute, prepared for the Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency (EPA), has shown that roughly 72 million people are exposed to tetrachloroethylene at an estimated average concentration greater than 0.01 ppb or 0.068 ug/m^3.

The chemical structure of tetrachloroethylene is shown below.



The current threshold limit value for tetrachloroethylene in the United States is 100 ppm (678 mg/m^3) (U.S. EPA 1980).

III. METABOLISM

Several investigators (NCI 1977a, b; Viola et al. 1971; Maltoni and Lefemine 1974; Creech and Johnson 1974; Waxweiler et al. 1976) have extensively studied the hepatotoxic, carcinogenic, and mutagenic potential of a number of chlorinated ethylene compounds including tetrachloroethylene. These studies have generated considerable interest in the metabolic pathways of these compounds by virtue of their ethylene bond and its subsequent conversion to a carcinogenic epoxide. The formation of an epoxide is catalyzed by the cytochrome P-450 dependent mixed-function oxidases of mammalian liver microsomes which oxidize the olefinic carbon-carbon double bond to an epoxide. The formation of an epoxide from chlorinated ethylenes has been documented by a number of investigators (Liebman and Ortiz 1968, 1970; Watabe and Maynert 1968; Maynert et al. 1970). Epoxides can potentially interact covalently with a variety of biological compounds to produce cellular necrosis, alteration of cellular metabolism, or carcinogenic or mutagenic lesions (Jerina and Daly 1974).

The formation of an epoxide intermediate for a chloroethylene compound was originally postulated by Powell (1945). Later, Yllner (1961) and Daniel (1963) speculated that tetrachloroethylene might be oxidized to an epoxide as an intermediate metabolite during its biotransformation. Recent interest in this hypothesis has resulted from findings that vinyl chloride is carcinogenic in man and animals (Lee and Harry 1974, Maltoni and Lefemine 1974, Creech and Johnson 1974). The mechanism of carcinogenic action of vinyl chloride was proposed by Van Duuren (1975), who suggested the formation of an epoxide intermediate, chloroethylene oxide, from vinyl chloride. A similar metabolic pathway and the formation of epoxide intermediates for structural homologues of vinyl chloride including tetrachloroethylene has also been proposed by Van Duuren (1977) and by

Corbett (1975). Tetrachloroethylene epoxide has not yet been detected as a first-step reaction product of tetrachloroethylene metabolism in vivo (U.S EPA 1980).

Kline et al. (1978) estimated a pseudo-first-order hydrolysis rate constant of 6.0×10^{-2} per minute for tetrachloroethylene epoxide in aqueous buffer (pH 7.4) at 37°C. The hydrolysis product was identified as trichloroacetic acid. Since the epoxide was in the presence of a large excess of water, the amount of epoxide was considered to be the only variable in the estimation of the hydrolysis rate constant. Hence, kinetics of the decomposition of tetrachloroethylene epoxide in water were treated as pseudo-first-order. However, it is possible that the degradation rate for tetrachloroethylene epoxide in aqueous buffer may not be indicative of the kinetics for tetrachloroethylene epoxide metabolism.

Yllner (1961) studied the metabolism of ^{14}C-labeled tetrachloroethylene in mice exposed by inhalation to 1300 mg/kg (calculated to body weight) for two hours. Over a 4-day period, 70% of the absorbed radioactivity was expired in air, 20% was excreted in the urine, and less than 0.5% was eliminated in the feces. Of the total urinary radioactivity, 52% was identified as trichloroacetic acid, 11% as oxalic acid, and a trace as dichloroacetic acid. No labeled monochloroacetic acid, formic acid, or trichloroethanol was found. However, 18% of the radioactivity was not extractable with ether, even after hydrolysis of the urine. These results suggest that tetrachloroethylene is metabolized to highly polar compounds.

Daniel (1963) administered single doses of ^{36}Cl-labeled tetrachloroethylene to rats by gavage at doses of 1.75 uCi to one Wistar rat and 13 uCi to four Wistar rats, and found that excretion was largely of unchanged compound through the lungs, (half-time of expiration was 8 hours).

Approximately 98% of the radioactivity in the low-dose animal was recovered in expired air 2 days post-treatment. Only 2% (approximately) of the radioactivity from both doses was excreted in the urine during 18 days following treatment, and equimolar proportions of trichloroacetic acid and inorganic chloride were the only metabolites detected. No radioactivity was detected in feces. Trichloroacetic acid has since been observed to be a urinary metabolite of tetrachloroethylene in humans (Monster and Houtkooper 1979). These studies demonstrate the occurrence of a metabolic breakdown of a tetrachloroethylene to trichloroacetic acid, in which transfer of a chlorine from one carbon to another had taken place. The most likely pathway for formation of trichloroacetic acid would be via epoxidation of the double bond. The resulting epoxide is known to be chemically unstable and rearranges spontaneously to trichloroacetaldehyde which is further oxidized to trichloroacetic acid.

Leibman and Ortiz (1970) summarized possible metabolic pathways of tetrachloroethylene. The formation of tetrachloroethylene epoxide by the hepatic mixed-function oxidase system may be followed by hydration of the epoxide to tetrachloroethylene glycol. Due to the symmetric arrangement of the epoxide and the glycol intermediates, rearrangement of either would yield trichloroacetyl chloride, which hydrolyzes rapidly to trichloroacetic acid.

Evidence for the role of the microsomal mixed-function oxidase system in the metabolism of tetrachloroethylene was shown by Moslen et al. (1977). Rats pretreated with phenobarbital or Aroclor 1254 (inducers of the hepatic mixed-function oxidase system) showed a significant increase in total trichlorinated urinary metabolites and trichloroacetic acid excretion following a single oral administration of 0.75 ml/kg tetrachloroethylene. Although, as described previously, trichloroacetic acid has been observed by several investigators to be a urinary metabolite of tetrachloroethylene, the excretion of total trichloro compounds, as measured by the Fujiwara colorimetric reaction after oxidation, exceeded that of trichloroacetic acid. In some cases this was assumed to be trichloroethanol. In other studies, that portion that was not trichloroacetic acid could not be demonstrated to be trichloroethanol.

Pegg et al. (1979) have studied the disposition of [^{14}C]tetrachloroethylene following oral and inhalation exposure in rats. In this study (Tables 1 and 2), tetrachloroethylene was administered to adult male Sprague-Dawley rats by gavage (1 or 500 mg/kg) or by inhalation (10 or 600 ppm, 6-hour duration). Within 72 hours following oral administration of 1 mg/kg or inhalation of 10 ppm [^{14}C]tetrachloroethylene, approximately 70% of the radioactivity was excreted in expired air as tetrachloroethylene, 26% as $^{14}CO_2$ and nonvolatiles in urine and feces, and 3 to 4% remained in the carcass. After oral administration of 500 mg/kg or inhalation of 600 ppm [^{14}C]tetrachloroethylene, 89% of the radioactivity was recovered in expired air as tetrachloroethylene, 9% as $^{14}CO_2$ and urinary and fecal metabolites, and 1 to 2% remained in the carcass. The major urinary metabolite of tetrachloroethylene was identified as oxalic acid. Pulmonary elimination of tetrachloroethylene was monophasic with a half-life (t1/2) of approximately 7 hours independent of dose or route of administration. Radioactivity remaining in the carcass 72 hours after exposure by either route was primarily distributed within liver, kidneys, and fat tissue. In liver, 85 to 90% of the total radioactivity was cleared within 72 hours following inhalation exposure to 10 or 600 ppm (Table 3). (Nonextractable radioactivity, either bound or incorporated into hepatic macromolecular material, was cleared at a slower rate).

TABLE 1. RECOVERY OF RADIOACTIVITY 72 HOURS FOLLOWING ORAL ADMINISTRATION OF TETRACHLORO[1,2-^{14}C]ETHYLENE TO RATS[a]

(Pegg et al. 1979)

	Recovery[b]			
	1 mg/kg		500 mg/kg	
	umol eq	%[c]	umol eq	%[c]
Expired air				
Tetrachloroethylene	1.05 ± 0.00	71.5 ± 1.4	667.31 ± 22.72	89.9 ± 0.3
$^{14}CO_2$	0.04 ± 0.01	2.5 ± 0.4	3.44 ± 0.36	.5 ± 0.1
Urine	0.24 ± 0.00	16.5 ± 0.4	34.48 ± 2.40	4.6 ± 0.2
Feces	0.09 ± 0.02	6.2 ± 1.4	29.08 ± 4.01	3.9 ± 0.4
Carcass	0.05 ± 0.00	3.3 ± 0.3	8.50 ± 0.66	1.2 ± 0.1
Total	1.46 ± 0.02		742.79 ± 27.75	

---

[a] One or 500 mg/kg tetrachloro[^{14}C]ethylene was administered to rats by oral gavage in 1.0 ml/kg corn oil. Animals were maintained in metabolism cages and killed 72 hours after exposure.

[b] Each value represents the mean (± S.E.) of data from three rats.

[c] Percentage of total recovered radioactivity.

TABLE 2. RECOVERY OF RADIOACTIVITY 72 HOURS FOLLOWING INHALATION EXPOSURE OF RATS TO TETRACHLORO[1,2-^{14}C]ETHYLENE TO RATS[a]
(Pegg et al. 1979)

	Recovery[b]			
	10 ppm		600 ppm	
	umol eq	%[c]	umol eq	%[c]
Expired air				
Tetrachloroethylene	6.08 ± 0.44	68.1 ± 2.7	412.38 ± 7.60	88.0 ± 0.3
$^{14}CO_2$	0.32 ± 0.05	3.6 ± 0.7	3.25 ± 0.17	0.7 ± 0.0
Urine	1.66 ± 0.12	18.7 ± 1.2	27.40 ± 1.68	6.0 ± 0.1
Feces	0.46 ± 0.02	5.2 ± 0.4	14.24 ± 0.75	3.1 ± 0.2
Carcass	0.38 ± 0.06	4.3 ± 0.9	10.07 ± 0.54	2.2 ± 0.2
Total	8.91 ± 0.33		467.05 ± 8.11	

[a] Rats were exposed to 10 or 600 ppm tetrachloro[^{14}C]ethylene for 6 hours and maintained for 72 hours after exposure in metabolism cages.

[b] Each value represents the mean (± S.E.) data from three rats.

[c] Percentage of total recovered radioactivity.

TABLE 3. DISTRIBUTION OF RADIOACTIVITY IN RAT TISSUES 72 HOURS FOLLOWING ORAL OR INHALATION EXPOSURE TO TETRACHLORO[1,2-^{14}C]ETHYLENE[a]
(adapted from Pegg et al. 1979)

	Oral		Inhalation	
Tissue	1 mg/kg	500 mg/kg	10 ppm	600 ppm
Liver	0.0008 ± 0.0001	0.097 ± 0.013	0.0047 ± 0.0006	0.096 ± 0.001
Kidney	0.0004 ± 0.0000	0.137 ± 0.016	0.0018 ± 0.0002	0.167 ± 0.002
Fat	0.0006 ± 0.0000	0.272 ± 0.061	0.0018 ± 0.0002	0.082 ± 0.015
Brain	ND[b]	ND	ND	ND
Lung	0.0002 ± 0.0000	0.092[1][c]	0.0012[2][c]	0.066 ± 0.002
Heart	0.0001 ± 0.0000	0.051[1][c]	0.0009[1][c]	0.045 ± 0.004
Adrenal	0.0005[2][c]	ND	ND	ND

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[a] Animals were sacrificed 72 hours after exposure and tissue samples frozen in liquid nitrogen. Random samples of crushed tissue were taken for analysis. Results are expressed in umol eq/g. Each value represents the mean (± S.E.) of data from three rats.

[b] ND=tissue concentration less than detection limit (2 x background).

[c] One or two of three determinations had values below the detection limit. Number in brackets represents number of values above detection limit.

The tissue concentration of nonextractable radioactivity was dependent upon body burden and metabolic capacity, but apparently not upon route of administration (Table 4). Thus, the data indicate that disposition of tetrachloroethylene is a saturable, primarily dose-dependent process in rats.

Recently, studies on the pharmacokinetic and macromolecular interaction of tetrachloroethylene in rats and mice were described by Schumann et al. 1980. This study was conducted in B6C3F1 mice and Sprague-Dawley rats in an attempt to explain mechanistically, the sensitivity of the mouse and the resistance of the rat to tetrachloroethylene-induced hepatocellular carcinoma. Mice were found to metabolize 8.5 and 1.6 times more tetrachloroethylene per kg of body weight than rats following inhalation of 10 ppm for 6 hours or a single oral dose of 500 mg/kg of [^{14}C]tetrachloroethylene, respectively. Since the initial metabolism of tetrachloroethylene is an activation process, the increased extent of metabolism in the mouse resulted in a greater extent of irreversible binding of radioactivity in hepatic macromolecules (only in proteins) of the mouse compared to that in the rat after inhalation of 10 ppm or 600 ppm for 6 hours, or a single oral dose of 500 mg/kg of [^{14}C]tetrachloroethylene. Repeated oral administration of tetrachloroethylene for 11 days resulted in histopathological changes in the liver of mice at doses as low as 100 mg/kg/day, while minimal treatment-related effects were observed in the livers of rats only at the 1000 mg/kg/day level. Approximately a twofold increase in hepatic DNA synthesis, indicating hepatic regeneration, was observed in mice but not in rats after repeated oral administration of tetrachloroethylene at dose levels that are tumorigenic to mice in lifetime studies. The authors stated, without presenting their data, that no significant direct interaction of tetrachloroethylene with hepatic DNA in mice was observed at times of peak hepatic macromolecular binding. Based on this, Schumann et al. (1980) suggest that hepatic tumors

TABLE 4. EFFECTS OF DOSE AND ROUTE OF ADMINSTRATION ON APPARENT BINDING OF TETRACHLORO[1,2-^{14}C]ETHYLENE TO RAT HEPATIC MACROMOLECULES[a]
(Pegg et al. 1979)

Route of Administration	Exposure	Body Burden[b] (mg eq/kg)	Metabolized[c] (umol eq)	Bound (umol eq/g liver protein)	$\frac{\text{Bound}}{\text{Metabolized}} \times 100$
Oral	1 mg/kg	1.12 ± 0.01	0.41 ± 0.03	0.0035 ± 0.0003	0.83 ± 0.05
Oral	500 mg/kg	522.73 ± 1.30	73.92 ± 4.98	0.4321 ± 0.0477	0.59 ± 0.11
Inhalation	10 ppm	5.51 ± 0.25	2.82 ± 0.16	0.0245 ± 0.0022	0.87 ± 0.09
Inhalation	600 ppm	292.87 ± 5.18	55.46 ± 0.44	0.04029 ± 0.0222	0.72 ± 0.04

[a] Seventy-two hours following oral or inhalation (6 hr) exposure tissue samples were homogenized and precipitated by addition of TCA. The precipitate was washed repeatedly, solubilized in 1N KOH, and assayed for radioactivity and protein. Each value represents the mean (± S.E.) of data from at least three rats.

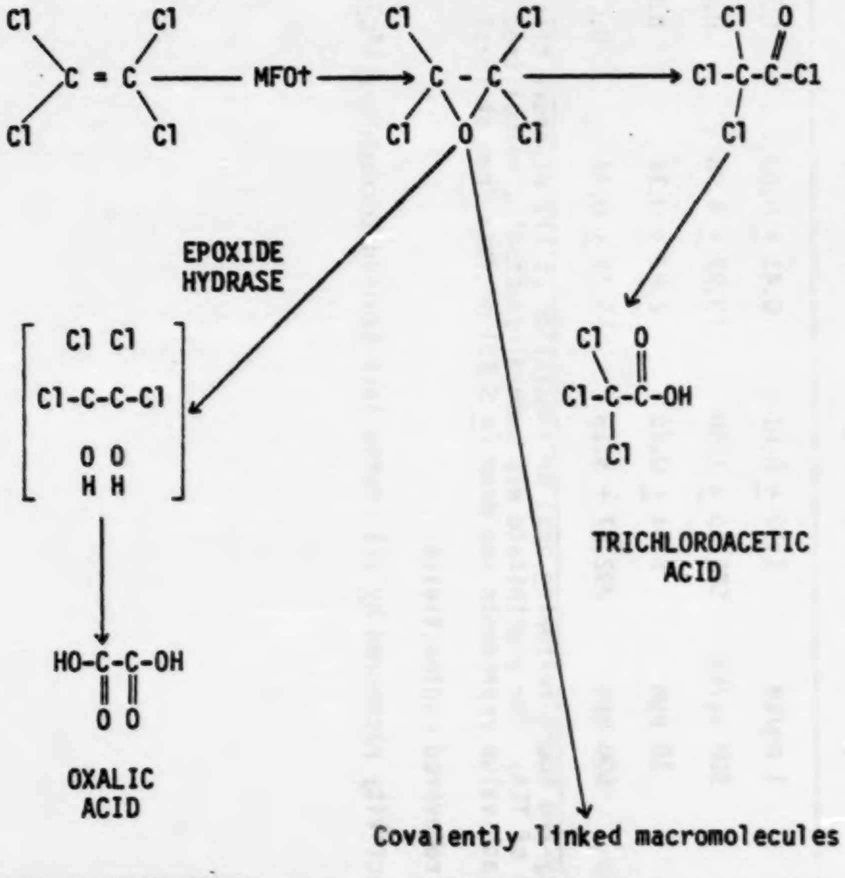
[b] Total recovered radioactivity.

[c] Radioactivity recovered by all routes less expired tetrachloro[^{14}C]ethylene.

are induced in B6C3F1 mice by recurrent cytotoxicity which enhances the spontaneous incidence of liver tumors in this highly susceptible strain of mouse, thereby inferring that the development of liver tumors in the mouse results from a nongenetic (epigenetic) rather than genetic mechanism.

The proposed metabolic pathway (Figure 1), based on a review of the literature, indicates that tetrachloroethylene epoxide is a highly reactive, transitory intermediate, having carcinogenic potential. (The information on tetrachloroethylene metabolism is also summarized in U.S. EPA 1980).

Figure 1. Proposed metabolism of tetrachloroethylene.*


MFO†
EPOXIDE HYDRASE
TRICHLOROACETIC ACID
OXALIC ACID
Covalently linked macromolecules

---

*Dichloroacetic acid, ethylene glycol, and trichloroethanol have been reported to be metabolites of tetrachloroethylene.

†MFO = mixed-function oxidases.

FATE OF TETRACHLOROETHYLENE IN HUMANS

A study of the absorption of the tetrachloroethylene vapor through intact human skin (Riihimaki and Pfaffli 1978) indicated that low amounts of the chemical were absorbed by three male individuals at an exposure level of 600 ppm (4,069 mg/m^3 air) for 3.5 hours. The subjects exercised for 10 minutes at half-hour intervals during exposure. Respirators were worn to prevent pulmonary exposure. Tetrachloroethylene concentrations in blood and expired air were determined for 20 and 50 hours post-exposure, respectively.

Blood levels of tetrachloroethylene peaked at approximately 700 ug/l by the end of exposure and following treatment declined rapidly to approximately 100 ug/l by 6 hours with a slight further reduction to 90 ug/l by 20 hours. Amounts of tetrachloreothylene in expired air attained a maximal level of approximately 60 ug/l by the end of exposure which sharply declined to a level of 1 ug/l by 10 hours post-treatment which was sustained for an additional 40 hours.

The total average amount of tetrachloroethylene eliminated in expired air during the 50-hour monitoring period was estimated to be 281.2 umol (46.6 mg). Based on an assumption that the amount in expired air represented 98% of the absorbed tetrachloroethylene, percutaneous uptake of tetrachloroethylene was calculated to be 286.9 umol (47.6 mg). At the exposure level of 600 ppm (3.5 hours) used in this study, the authors calculated a theoretical estimate of pulmonary absorption of tetrachloroethylene as the product of (inhaled concentration - exhaled concentration) x ventilation x length of exposure. Assumptions made for this calculation included a ventilation rate of 10 l/min and a retention of 50%. The theoretical total pulmonary absorption of tetrachloroethylene was calculated to be 25.45 mmol (4,221 mg). Thus, percutaneous absorption was calculated to be 1.1% of pulmonary absorption. Similarly, this theoretical relationship between percutaneous and pulmonary absorption suggests that percutaneous exposure to 600 ppm tetrachloroethylene is equivalent to pulmonary exposure to 6.6 ppm tetrachloroethylene.

Ikeda (1977) described the urinary half-life of tetrachloroethylene metabolites in humans who were occupationally exposed to the vapor. The urinary half-life of tetrachloroethylene averaged 144 hours; 190.1 ± 32.9 hours for females (six subjects exposed 8 hours/day, 5 days/week, 10 to 20 ppm), and 123.3 ± 23.5 hours for males (six subjects exposed 8 hours/day, 5 days/week, 30 to 100 ppm). The half-life of tetrachloroethylene eliminated via exhalation was calculated to be 65 hours.

Gruberan and Fernandez (1974) followed the course of tetrachloroethylene elimination in expired air in 25 human subjects exposed to 50 to 150 ppm (339 to 1,017 mg/m^3 air) for up to 8 hours. Using the data to develop a mathematical model to predict the metabolic fate of tetrachloroethylene *in vivo*, these investigators concluded that fatty tissues would show the slowest rate of tetrachloroethylene depletion, and a biological half-life of 71.5 hours for fat stores of tetrachloroethylene has been estimated. Fernandez et al. (1976) observed that essentially complete elimination of tetrachloroethylene from human subjects required 2 weeks following an 8-hour exposure to 100 ppm (678 mg/m^3 air). Stewart et al. (1974) also found that tetrachloroethylene was slowly eliminated from 19 human volunteers exposed to varying concentrations (20 to 150 ppm) of tetrachloroethylene for 5 weeks. With repeated daily exposures, tetrachloroethylene has been shown to accumulate in body tissues, especially lipids (Stewart et al. 1974, Gruberan and Fernandez 1974).

The fate of tetrachloroethylene in humans, mice, and rats after various routes of exposure is presented in Table 5 as summarized from Lapp et al. (1979) and Bolanowska and Golacka (1972). These data suggest that species differences in tetrachloro metabolism do exist.

TABLE 5. FATE OF TETRACHLOROETHYLENE[a]

				Excretion			
				Unchanged	Metabolized		
Species	Route	Intake	Acutely Retained by Body (%)	Lung	Urine	Skin	Feces
Man	Inhalation	1 breath (5 mg)		15%/1 hour	2.8%		
Man	Inhalation	87 ppm/3 hr	50	< 50%			
Man	Inhalation	194 ppm/187 min		< 30 ppm at 1 hr			
Man	Inhalation	390 ppm/6 hr	62[b]	25%	< 10%	0.02%	
Man	Inhalation	395 ppm/3.5 hr		85 ppm at 1 hr			
Man	Thumb immersion			maximum 6.6 ppm			
Mice	Inhalation	1300 mg/kg		70%	20%		< 0.5%
Rats	Inhalation	200 ppm/8 hr			5.3 mg/kg		
Rats	Oral	1.75 and 13 uCi		97.9%	1.6-2.1 (18 days)		

[a] Lapp et al. 1979.

[b] Bolanowska and Golancka 1972.

IV. MUTAGENICITY* AND CELL TRANSFORMATION

Information concerning the mutagenicity of tetrachloroethylene has been obtained from six bacterial studies, one yeast study, and two *in vivo* mammalian cytogenetic studies. These reports are discussed below and are summarized in Table 6.

Henschler (1977) reported that tetrachloroethylene was not mutagenic when tested in *Escherichia coli* K12 with metabolic activation (liver microsomal fraction prepared from phenobarbital-induced mice). The nonmutagenic effect reported for tetrachloroethylene, was theorized to be due to the formation of a stable symmetrical configuration of the epoxide formed from this compound. The possibility of a highly reactive intermediate is not reduced by this study in that the stable epoxide of tetrachloroethylene hypothesized by Henschler is based on structure-activity relationships and mutagenicity data. Henschler (1977) indicated that, because of primary toxicity (cell death), the *Salmonella* test system was not suitable to evaluate the mutagenicity of some chlorinated ethylenes, including tetrachloroethylene. This report is difficult to evaluate because the revertant count data (experimental and control) and the details of the protocol are not provided. It appears, however, that the conclusions presented in this report are actually based on data derived from the study by Greim et al. (1975).

Greim et al. (1975) reported that tetrachloroethylene was nonmutagenic for *Escherichia coli* K12 (genetic markers: gal^-, arg^-, nad^-, and MtR) after a treatment time of 2 hours at a concentration of 0.9 mM (survival 99 ± 1%) in the absence and presence of metabolic activation (phenobarbital-induced mouse liver microsomal fraction plus NADPH cofactors). Some deficiences in the study design and reporting of the results reduce the weight of the negative

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*Prepared by the Reproductive Effects Assessment Group.

TABLE 6. MUTAGENICITY TESTS OF TETRACHLOROETHYLENE

A. BACTERIA

Reference	Test System	Strain	Activation System	Dose	Result	Comments
Bartsch et al. 1979	*Salmonella* test: plate incorporation assay	TA 100	Phenobarbital-induced male OF-1 mouse liver S9 mix	Concentrations up to 4 x 10^{-3}M (purity 99.7%, impurities not reported)	Reported as negative	1. Revertant count data were not presented 2. No concurrent positive control which requires metabolic activation 3. Exact concentrations tested not given 4. Toxic effects reported for concentrations above 5 x 10^{-4}M 5. Only single tester strain used
Cerna and Kypenova 1977	*Salmonella* test: spot test	TA 1950 TA 100 TA 1951 TA 98 TA 1952 TA 1535 TA 1538		100%, 10%, 1% (DMSO as solvent) in an amount of 0.05 ml/plate	Reported as positive (in undiluted form)	1. An abstract with no protocol and data presented 2. Purity of test material not reported
	Host-mediated assay (female ICR mice were host)	TA 1950 TA 1951 TA 1952		Reported as doses representing LD_{50} and one half the LD_{50}	Reported as positive	1. 1 and 2 as above 2. Authors reported no dose-response
Greim et al. 1975	Mutation to prototrophy in *Escherichia coli*: liquid suspension	K12, gal-nad-arg-MTR	Phenobarbital-induced mice liver S9 mix	0.9mM, 2 hr treatment (survival 99+1%) purity reported as analytical grade, impurities not reported	Reported as negative	1. Single nontoxic dose tested 2. Not reported if test was repeated to confirm negative results 3. Revertant count data not given

(continued on following page)

TABLE 6. (continued)

A. BACTERIA

Reference	Test System	Strain	Activation System	Dose	Result	Comments
Henschler 1977	Mutation to prototrophy in *Escherichia coli*	K12, gal- arg- nad- MTR	Phenobarbital-induced mice liver S9 mix	0.6 mM	Reported as negative	1. Details of the protocol were not presented 2. Toxicity not reported for dose tested 3. Report does not state if test repeated to confirm negative findings 4. Revertant count data not reported 5. Purity of test material not reported
Margard 1978	*Salmonella* test: plate incorporation	TA 1535 TA 1537 TA 1538 TA 98 TA 100	Aroclor 1254 induced male Sprague-Dawley rat liver S9 mix	Stabilized and nonstabilized (purified) 1.0, 0.5, 0.1, 0.01, ml/plate, dissolved in DMSO Formulation of Stabilized Material (%) epichlorohydrin 0.07 N methyl morpholine 0.007 beta-hydroxy proponitrile 0.07 hydroquinone monomethyl ether 0.01	Nonstabilized was negative and stabilized was positive	1. Actual revertant counts for each plate not given, therefore the variation per dose tested is not known; the original data has been requested 2. Actual concentrations of the test material tested not reported
Taylor 1977	*Salmonella* test:				Reported as negative	1. Interoffice memo, no details of protocol and data not presented

(continued on following page)

TABLE 6. (continued)

B. YEAST

Reference	Test System	Activation System	Concentration (mM)	Survival (%)	Response/10^6 Survivors				Comments
						ade-2			
					trp-5 conversion	Recombination	Total genetic alterations	ilv-1 Revertants	
Callen et al. 1980	Gene conversion, mitotic recombination and gene reversion in *Saccharomyces cerevisiae* D7: liquid suspension	*in vivo* cytochrome P450-dependent monooxygenase system	0	100	14	330	3,000	2.9	1. No concurrent positive controls 2. Tetrachloroethylene contained 0.01% thymol as stabilizer (no thymol control)
			4.9	84	19	530	4,700	3.8	
			6.6	58	83	5260	26,800	not determined	
			8.2	< 0.01	--	--	----		

(continued on following page)

TABLE 6. (continued)

C. MAMMALIAN *IN VIVO* CYTOGENETICS

Reference	Test System	Strain	Dose	Result	Comment
Cerna and Kypenova 1977	Acute and subacute bone marrow assay	Female ICR mice	Acute-dose level 1/2 LD_{50} Subacute - five injections in 24 hour intervals (dose in one injection equal 1/6 LD_{50})	Reported as negative	1. An abstract with no details of protocol and cytogenetic data not presented 2. Purity of test material not reported
Rampy et al. 1978	Chronic study: bone marrow assay	Sprague-Dawley rats, male and female	300 or 600 ppm 6 hours/day, 5 days/week for one year by inhalation	Reported as negative for males, data for females considered by authors to be insufficient for clear interpretation	1. The number of scorable chromosome spreads for females reported as very low 2. Number metaphases scored per animal not given 3. Details of the cytogenetic protocol and cytogenetic data were not included in the report 4. Appears that not using exposure level at or near the maximum tolerated dose

Formulation	Liquid volume (%)
trichloroethylene	3 ppm
hexachloroethane	<12 ppm
carbon tetrachloride	2 ppm
4-methyl morpholine	44 ppm
nonvolatile residue	2 ppm
perchloroethylene	balance

conclusion: 1) only one concentration was evaluated, 2) revertant count data (experimental and control) were not reported, and 3)it is not stated whether or not the test was repeated to confirm the negative results.

Bartsch et al. (1979) investigated the mutagenicity of a number of haloethylenes including tetrachloroethylene. Tetrachloroethylene was evaluated in a plate incorporation assay. Negative results were reported with concentrations up to 4 x 10^{-3} M tetrachloroethylene using TA 100 in the presence of liver-enzyme activation (liver microsomal fraction prepared from phenobarbital-induced mice), with and without NADPH cofactors. However, concentrations above 5 x 10^{-4} M were reported as toxic to bacteria. Revertant count data were not presented to support the statement of nonmutagenicity. Because only a single Salmonella strain was used, the potential mutagenicity of the test material is not considered to be adequately examined in this system.

Taylor (1977) reported in an interoffice memo that tetrachloroethylene was nonmutagenic in Salmonella. The details of the protocol and data were not available for evaluation.

Cerna and Kypenova (1977) observed increased mutagenic activity in Salmonella typhimurium treated with tetrachloroethylene. Tetrachloroethylene was reported to induce both base-pair substitution and frameshift mutations in the absence of metabolic activation in a spot test. These authors also reported that in the host-mediated assay using tester strains TA 1950, TA 1951, and TA 1952, tetrachloroethylene induced significant increases in the number of revertants at dosage levels reported as representing the LD_{50} andone-half of the LD_{50}. The authors indicated that no dose-response was observed. This report was an abstract which did not provide details of the protocol, did not present the data, and did not report the purity of the test material. Thus, the acceptability of the test results could not be determined.

Margard (1978) tested both stabilized and unstabilized tetrachloroethylene in the Ames plate incorporation assay using TA 1535, TA 1537, TA 1538, TA 98, and TA 100. The unstabilized test material was described as purified tetrachloroethylene and the stabilized material was identified as an industrial, degreasing grade of tetrachloroethylene containing 0.07% epichlorohydrin and other stabilizer components (Schlossberg 1981, see Table 1 for formulation). Positive responses were reported using the frameshift sensitive strains TA 1538 and TA 98, and the base-pair substitution sensitive strain TA 100 (also sensitive to certain frameshift acting mutagens) with 0.1 ml per plate of stabilized tetrachloroethylene, both in the presence and absence of liver enzyme activation (S9 mix prepared from livers of Aroclor 1254-induced male Sprague-Dawley rats). It should be stressed, however, that the stabilized test material contained epichlorohydrin, which has been shown to be strongly mutagenic in Salmonella (McMahon et al. 1979, Anderson et al. 1978). Negative results were observed using stabilized test agent in strains TA 1535 and TA 1537 both with and without S-9 activation.

Unstabilized tetrachloroethylene (purified) was not detected as mutagenic in the five tester strains in either the presence or absence of metabolic activation up to 0.1 ml per plate (actual concentration not given).* Because stabilized tetrachloroethylene appears to produce point mutations in Salmonella and "pure" tetrachloroethylene appears not to be mutagenic, this suggests that an impurity (epichlorohydrin) may be producing the observed mutagenic activity in the stabilized test material. However, with respect to mutagenicity testing of highly purified tetrachloroethylene, it should be noted that tetrachloroethylene is a chlorinated chemical, and that several chlorinated chemicals (e.g., carbon tetrachloride, DDT) have not been properly evaluated in the *Salmonella*/microsome test (McCann et al. 1975, Ames 1979). It also should be emphasized that a negative result in a bacterial point mutation test system does not preclude the mutagenic activity of the chemical evaluated. For example, several factors such as the toxicity, solubility, and volatility of the test agent, differences between *in vitro* liver enzyme activation and *in vivo* metabolic activation, and the relative reactivity (e.g., highly reactive intermediates) of the metabolites could result in a chemical not being detected as positive in an *in vitro* test system.

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*Margard indicated in a personal communication that precautions were taken to prevent evaporation of test material, but did not confirm this in writing.

Callen et al. (1980) evaluated the ability of tetrachloroethylene (containing 0.01% thymol as a stabilizer) and six other halogenated aliphatic hydrocarbons to cause gene conversion at the *trp-5* locus, mitotic recombination at the *ade-2* locus, and reversion at the *ilv-1* locus in *Saccharomyces cerevisiae* D7. In this organism, a marginal increase in the frequency of gene conversion (19 convertants/10^6 survivors versus 14 convertants/10^6 survivors in control) and mitotic recombination (530 mitotic recombinants/10^6 survivors versus 330 mitotic recombinants/10^6 survivors in the control) was produced by a 1-hour treatment at 4.9 mM (84% survival). When the concentration of tetrachloroethylene was increased to 6.6 mM (58% survival), increases in gene conversion and mitotic recombination (83 convertants/10^6 survivors and 5260 mitotic recombinants/10^6 survivors, respectively) were found. A marginal increase in reversion was observed at 4.9 mM (3.8 revertants/10^6 survivors versus 2.9 revertants/10^6 survivors in control). The reversion frequency was not determined at 6.6 mM. The results suggest that tetrachloroethylene (with 0.01% thymol) is genetically active in yeast. However, these results should be confirmed by repeating the assay using at least an additional concentration between the high and low concentrations tested to demonstrate a dose-response. If thymol is used as a stabilizer, a concurrent thymol control should be included to address the possibility of a mutagenic impurity. It should be noted that because this yeast strain contains a cytochrome P450-dependent monooxygenase system for metabolism, it is possible that tetrachloroethylene is being activated by the organism. This yeast activation system is probably more sensitive for metabolites that are particularly unstable and reactive than an in vitro activation system, because metabolic activation is occurring within the cell in much closer proximity to the nucleus, whereas in vitro S9 liver activation occurs outside the cell.

Schumann et al. (1980) reported that there was no detectable binding of ^{14}C-labeled tetrachloroethylene (99% pure) to DNA when mice were treated by inhalation at 600 ppm for 6 hours or given 500 mg/kg orally. The results of this study are difficult to interpret because the specific activity of the ^{14}C-labeled tetrachloroethylene was low and the data were not shown.

Rampy et al. (1978), in a chronic rat study, examined three male and three female rats for chromosome aberrations after the animals had been exposed to 300 or 600 ppm (2.03 or 4.07 mg/l) tetrachloroethylene formulation (see Table 6 for formulation) by inhalation 6 hours/day, 5 days/week, for one year. The authors reported no chromosome or chromatid aberrations in the bone marrow cells of male rats, and indicated that the data for female rats were inadequate for a clear interpretation because of the low number of scorable metaphases. In addition, it does not appear that the highest exposure level is near the maximum tolerated dose (MTD) for females because no weight loss was reported and no mortality was observed. Although there were no weight losses in males, the MTD may have been approached because significant increases in mortality above control values were observed at the highest dose. However, it should be noted that it is not apparent that the investigators determined the toxicity of the test material to arrive at a MTD for this study since the dosage levels were based on the threshold limit value of 100 ppm for tetrachloroethylene.

Cerna and Kypenova (1977) reported in an abstract that male mice (ICR) given an acute intraperitoneal dose or dosed intraperitoneally for five applications did not show cytogenetic effects in the bone marrow cells. Details of the protocol and the cytogenetic data were not available for an evaluation. In addition, the purity of the chemical was not reported.

Ikeda et al. (1980) studied peripheral lymphocytes cultured from ten workers (seven males and three females) occupationally exposed to technical grade tetrachloroethylene (impurities not known) for an increased incidence of chromosome aberrations (structural and numerical), sister chromatid exchanges, and for an altered mitotic index. The workers were divided into high (Group 1) and low (Group 2) exposure groups. Group 1 consisted of six workers (five males and one female, 20 to 66 years of age) from a degreasing workshop that had a geometric mean exposure of 92 ppm (range 30-220 ppm). The five males of Group 1 had work histories of 10 to 18 years, whereas the one female had worked in the degreasing shop for only 1 year. Group 2 included four workers (two males and two females, 17 to 31 years of age) from a support department with a shorter work history (3 months to 3 years) and with an exposure range of 10 to 40 ppm. The control group consisted of six males and five females. The authors did not indicate that this was a matched control. There was no statistically significant difference ($P < 0.05$) between the incidence of chromosome aberrations (structural and numerical) and sister chromatid exchanges between the exposed workers and control group.

In summary, tetrachloroethylene has not been clearly demonstrated to cause point mutations in bacteria. However, a negative result in a particular bacterial system does not preclude the mutagenic activity of a chemical in other organisms. Only two positive bacterial reports were found in the available literature and both utilized the Salmonella system. One was an abstract by Russian authors where the purity of the test material was not reported and the data were not provided to substantiate the reported results (Cerna and Kypenova 1977). The other indicated that only stabilized test material (the mutagen epichlorohydrin reported to be present) was active and the nonstabilized test material (purified) was not active (Margard 1978). The cytogenetic studies also have been negative (however, there were no available studies on the ability of tetrachloroethylene to cause spindle effects). There is suggestive evidence in yeast, however, that tetrachloroethylene may be genetically active. This positive response needs to be confirmed by re-examining the genetic activity of tetrachloroethylene in yeast using "pure" chemical and a concentration range that would give at least four points (including the zero point) on a dose-response curve. Therefore, to date, the bacterial tests appear to be negative and the positive result in yeast does not permit a final judgment on the mutagenicity of tetrachlororethylene but emphasizes the need for further studies to evaluate its potential mutagenicity.*

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*The Agency has recently received additional mutagenicity data for tetrachloroethylene (Beliles et al. 1980). The REAG is currently evaluating these data. It should be noted that these studies employed a 91.43% purity of tetrachloroethylene and that the 8.57% impurities present were not identified. Thus, unless information concerning the impurities is made available, positive conclusions would be considered as inconclusive.

CELL TRANSFORMATION

Price et al. (1978) exposed Fischer rat embryo cell cultures (F1706, subculture 108) to tetrachloroethylene liquid at concentrations of 97 and 970 uM (1 uM = 165.85 ug) for 48 hours. According to the authors, the subculture used did not require exogenous murine type "C" RNA virus and was free of known infectious virus; however, the cells did contain genetic information of the Rauscher leukemia virus. Tetrachloroethylene was diluted with growth medium to yield the appropriate doses. The tetrachloroethylene sample, obtained from Eastman Kodak, would probably have been 98 to 99% pure and stabilized with 0.5% ethanol and/or 0.1% propylene oxide (personal communication with Eastman Kodak Company). The cells were grown in Eagles minimum essential medium in Earle's salts supplemented with 10% fetal bovine serum, 2mM L-glutamine, 0.1 mM nonessential amino acids, 100 U penicillin, and 100 ug streptomycin per ml. Quadruplicate cultures were treated at 50% confluency with each dose. After treatment, cells were cultured in growth medium alone at 37°C. Transformation of cells treated with the low- and high-dose of tetrachloroethylene was observed by 37 and 23 days of incubation, respectively, and was characterized by progressively growing foci composed of cells lacking contact inhibition and orientation. There was no transformation of cells grown in medium alone or in the presence of a 1:1000 acetone concentration by subculture 9 (81 days of incubation). The number of microscopic foci per three dishes with the low and high tetrachloroethylene doses was 178 and 147, respectively, in dishes inoculated with 50,000 cells from cultures treated four subcultures earlier and held for four weeks at 37°C in a humidified CO_2 incubator prior to staining.

Subcutaneous injection of cells treated with 97uM tetrachloroethylene five subcultures earlier produced local fibrosarcomas in 7/7 newborn Fischer 344 treatment. The ability of cells grown in growth medium alone and in the presence of 970 uM tetrachloroethylene to induce local fibrosarcomas was not determined; however, this tumor type did not develop in rats given cells grown in the presence of 1:1000 concentration of acetone. Exposure of cells to 3.7 x 10^{-1} uM 3-methylcholanthrene produced 124 microscopic foci per three dishes in the inoculation test described above by 37 days of incubation and local fibrosarcoma in 12/12 rats by 2 days following subcutaneous injection of cells. The exposure of 3-methylcholanthrene was attained by an initial dilution in acetone to 1 mg/ml followed by further dilution in growth medium to 0.1 ug/ml. The authors did not attempt a repeat of this study (personal communication with P. L. Price, Center for Disease Control, Atlanta).

It is understood that this cell line contains the genome of the Rausher leukemia virus, but there is no basis for minimizing the positive results, since the mode of action of tetrachloroethylene is not known (i.e., due to activation of virus).

V. TOXICITY

Toxic effects of tetrachloroethylene were reported in a recent review by the U.S. Environmental Protection Agency (1980) in a health assessment document which concludes that tetrachloroethylene causes central nervous system depression in animals. Signs of functional disturbances in animals, which are viewed as expressions of central nervous system depression, include abnormal weakness, intoxication, restlessness, irregular respiration, muscle incoordination, and unconsciousness.

Tetrachloroethylene is irritating to the eyes and skin. Its solvent action on natural oils causes defatting of the skin. Damage to the liver and/or kidney has been shown to occur in various animal species following exposure to tetrachloroethylene by various routes of administration including inhalation. Long-term inhalation exposure to tetrachloroethylene has been shown to cause changes in immunological response.

VI. CARCINOGENICITY

ANIMAL STUDIES

Two-long term animal bioassays have been performed to assess the carcinogenic potential of tetrachloroethylene. In one involving exposure of rats and mice to tetrachloroethylene by gavage, the National Cancer Institute (NCI) reported the induction of hepatocellular carcinomas in male and female mice, but concluded that the test with rats was inconclusive due to excessive mortality. In the other study, in which Sprague-Dawley rats were exposed to tetrachloroethylene by inhalation, the Dow Chemical Company (Rampy et al. 1978) reported no evidence for the carcinogenicity of the chemical. However, limitations in this study make it difficult to assess the carcinogenic potential of tetrachloroethylene.

National Cancer Institute Bioassay (1977b)

The tetrachloroethylene sample used in this bioassay was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. Analysis by gas-liquid chromatography and infrared spectroscopy yielded results indicating a purity > 99% with at least one minor impurity not identified in the report. Identification of the impurities in the test sample was not made (personal communication with the National Cancer Institute and Aldrich Chemical Company).

The carcinogenicity of tetrachloroethylene was tested in Osborne-Mendel rats and B6C3F1 mice. The initial age of the weanling animals was 25 days for the mice and 35 days for the rats. Two treatment groups consisted of 50 males and 50 females, and matched vehicle (corn oil) and untreated control groups comprised 20 animals of each sex. Selected dosage levels were those determined to be maximally tolerated in an 8-week subchronic study, i.e., a dosage that was not fatal and/or did not reduce body weight gain more than approximately 20%, and one-half maximally tolerated in an 8-week subchronic toxicity test. Time-weighted average doses (mg/kg/dose) in the chronic study were 941 and 471 for male rats, 949 and 474 for female rats, 1,072 and 536 for male mice, and 772 and 386 for female mice. Tetrachloroethylene was administered to the animals by gastric intubation in corn oil once each day, 5 days/week, for 78 weeks. During the final 26 weeks of treatment, doses were administered to rats in a cyclic pattern of 1 week without treatment followed by 4 weeks with treatment. Body weights and food consumption were obtained weekly for the first 10 weeks and monthly thereafter. Mice and rats were permitted to survive an additional 12 and 32 weeks after treatment, respectively, until sacrifice.

Each animal was submitted to extensive gross and microscopic examinations. Specified organs, plus any other tissue containing visible lesions, were fixed in 10% buffered formalin, embedded in paraplast, and sectioned for slides. Hematoxylin and eosin staining (H and E) was used routinely, but other stains were employed when needed. Diagnoses of observed tumors and other lesions were coded according to a modified Systematized Nomenclature of Pathology (SNOP) originally developed by the College of American Pathologists in 1965.

Tetrachloroethylene was found to be carcinogenic in mice in this study. Results summarized in Table 7 indicate that tetrachloroethylene induced highly statistically significant ($P < 0.001$) increases in the incidence of hepatocellular carcinoma in both sexes of mice in both treatment groups as compared to untreated controls or vehicle controls. The microscopic appearance of carcinomas was variable with some tumors composed of well-differentiated hepatocytes arranged in rather uniform hepatic cords and other lesions consisting of anaplastic cells often with inclusion bodies with vacuolated, pale cytoplasm. Mitotic figures were often present. In male mice, the first hepatocellular carcinomas were detected at 27 weeks in the low-dose group, 40

TABLE 7. INCIDENCE OF HEPATOCELLULAR CARCINOMAS IN B6C3F1 MICE FED TETRACHLOROETHYLENE
(National Cancer Institute 1977b)

Dose (mg/kg/day)[a]	Hepatocellular carcinomas	P values[b]
Male		
untreated	2/17 (12%)	
vehicle control	2/20 (10%)	
536	32/49 (65%)	$P < 0.001$
1072	27/48 (56%)	$P < 0.001$
Female		
untreated	2/20 (10%)	
vehicle control	0/20 (0%)	
386	19/48 (40%)	$P < 0.001$
772	19/48 (40%)	$P < 0.001$

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[a] Time-weighted average doses.

[b] Probability level (P-values) for the Fisher Exact Test comparison of dose groups with vehicle control group.

weeks in the high-dose group, and 90 and 91 weeks in vehicle and untreated control groups. In female mice, the first hepatocellular carcinomas were observed at week 41 in the low-dose group, week 50 in the high-dose group, and week 91 in the untreated control group. Metastases of hepatocellular carcinoma to kidneys in one untreated control male and lung in three low-dose males, one low-dose female, and one high-dose female occurred.

Toxic nephropathy in mice was apparent in 40/49 low-dose males, 45/48 high-dose males, 46/48 low-dose females, and 48/48 high-dose females. Control animals did not exhibit this lesion. Chronic murine pneumonia was also a frequently observed finding. A low incidence of bloating or abdominal distension was noted in treated animals during the second year of the study. Body weight gain was comparable between groups. Median survival times were greater than 90 weeks for control males, 78 weeks in low-dose males, 43 weeks in high-dose males, greater than 90 weeks in control females, 62 weeks in low-dose females, and 50 weeks in high-dose females.

In rats, toxic nephropathy, not found in control animals, was detected in 43/49 low-dose males, 47/50 high-dose males, 29/50 low-dose females, and 39/50 high-dose females. Treated rats gained less weight than controls, though the difference was slight with maximum reduction being 13% during the first year and 19% during the second year. Clinical signs apparent in treated animals included a hunched appearance and urine stains on the lower abdomen. Respiratory abnormalities, characterized by dyspnea, wheezing, and/or reddish nasal discharge were noted with increased incidence in all groups during aging of the animals and chronic murine pneumonia was diagnosed in $\geq$ 62% of the animals in each group. Median survival times were greater than 88 weeks in the control groups, 68 weeks in low-dose females, 66 weeks in high-dose females, 67 weeks in low-dose males, and 44 weeks in high-dose males. The survival was not adequate to support any conclusions about the carcinogenicity of tetrachloroethylene in rats.

In an attempt to characterize impurities present in the tetrachloroethylene product used in this study, documented chemical analyses of the test samples performed at the carcinogenicity testing laboratory were examined by the analytical department of the Diamond Shamrock Corporation (10/8/79 interoffice memorandum from E.A. Rowe to G.K. Hatfield, Diamond Shamrock Corporation, obtained with the documented chemical analyses by written communication with G.K. Hatfield, 1/28/81). Tetrachloroethylene samples used in the National Cancer Institute (NCI) (1977b) bioassay were stated to be unavailable for analysis at Diamond Shamrock; however, the analytical method with the same type of instrument and column used at the carcinogenicity testing laboratory was reproduced. Evaluation of the analytical method led to the conclusions presented in the previously mentioned 10/8/79 memorandum that the method could not distinguish epichlorohydrin from trichloroethylene and that the tetrachloroethylene product used in the NCI (1977b) bioassay could have contained one or both of these compounds as impurities. The documented chemical analyses show contaminant levels of 0.055%, 0.041%, and 0.010% in tetrachloroethylene samples analyzed at the beginning of the bioassay, at 1 year into the bioassay, and at 2 years into the bioassay, respectively. The conclusion in the previously described 10/8/19 memorandum is that the contaminant was probably epichlorohydrin since: 1) it was a commonly used stabilizer for tetrachloroethylene at that time; 2) a reported analysis by a competitor of Diamond Shamrock showed a maximum of 0.015% trichloroethylene in any tetrachloroethylene product manufactured in the United States, and 3) the decreased amount of impurity found in the tetrachloroethylene samples as the bioassay progressed suggests some decomposition in that, according to the experience of Diamond Shamrock, epichlorohydrin but not trichloroethylene levels would decrease during storage. Nonetheless, although the evidence provided by Diamond Shamrock indicates that epichlorohydrin was present in the tetrachloroethylene product used in the NCI (1977b) carcinogenicity study, the quantity of epichlorohydrin in the test material used in this study remains unclear. Furthermore, the different levels of unknown material shown in the documented chemical analysis may be due to the use of the indicated different lots possibly containing different amounts of impurities.

An estimate of the likelihood that the epichlorohydrin impurity in the tetrachloroethylene material used in the NCI experiment could have been large enough to account for the positive results can be obtained by considering the results of Lasken et al. (1980) who exposed rats to epichlorohydrin via inhalation. They found that 1/100 rats exposed to 30 ppm (0.115 mg/l air, equivalent to 13.2 mg/kg/day) of epichlorohydrin for 6 hours/day, 5 days/week, for 730 days developed squamous cell nasal carcinoma, compared with 0/50 in control animals.

The epichlorohydrin impurity in the NCI tetrachloroethylene high-dose male mice experiment was approximately 1,032 mg/kg/day x 0.041% = 0.42 mg/kg/day, from the discussion above. This is only about 0.42/13.2 ≃ 0.03 times the dose that gave an incidence of only 1/100 in the Laskin et al. rat experiment. Therefore, it is unlikely that epichlorohydrin impurities at the level estimated to be present in the NCI experiment could have contributed appreciably to the positive response.

A second carcinogenicity bioassay of tetrachloroethylene given orally to B6C3F1 mice and four strains of rats (Sherman, Fischer 344, Long-Evans, and Wistar) is being sponsored by the National Toxicology Program with completion expected by the end of 1981. The tetrachloroethylene sample used in this ongoing carcinogenicity bioassay does not contain detectable amounts of epoxide contaminants.

Dow Chemical Company Rat Inhalation Study (Rampy et al. 1978)

Two groups of weanling Sprague-Dawley (Spartan substrain) rats, each composed of 96 males and 96 females, were exposed to 600 ppm (4.07 mg/l air) or 300 ppm (2.03 mg/l air) of tetrachloroethylene 6 hours/day, 5 days/week, for 52 weeks. An untreated group of 192 males and 192 females served as untreated controls. Controls were not put in inhalation chambers but were in the treatment room during exposure. At the end of the treatment period of 52 weeks, animals were allowed to survive until sacrifice at 31 months. The composition of the test material (Lot A12282D) by gas chromatographic analysis was as follows: trichloroethylene, 3 ppm (liquid volume %); hexachloroethane, < 12 ppm; carbon tetrachloride, 2 ppm; 4-methyl morpholine, 44 ppm; nonvolatile residue, 2 ppm; tetrachloroethylene, balance. Exposure was done in 3.7 m^3 inhalation chambers with a dynamic airflow system. Analyses of tetrachloroethylene levels in the inhalation chambers during the treatment period revealed analytical concentrations (mean ± standard deviation) of 310 ± 32 ppm (244 analyses) and 592 ± 62 ppm (1,245 analyses). Analytical concentrations by infrared analysis, within ± 10% of nominal levels were achieved on 89.3% (low-dose) and 97.1% (high-dose) of the exposure days. Animals were evaluated for clinical toxic signs, body weight changes, urinalysis at 24 months, and hematology at 12 and 24 months. Survivors and decedents were given gross and histopathologic examinations. Bone marrow samples were taken from three males and three females in each group sacrificed at 1 year for cytogenetic evaluation.

Clinical signs of toxicity were not observed with the nominal concentrations of tetrachloroethylene used in this study. Mean body weight gains were similar among groups. Hematology and urine analyses showed no treatment-related effects of tetrachloroethylene. Mortality patterns are described in Table 8. Mortality in high-dose males was slightly greater compared to controls during months 5 to 24, and earlier onset of chronic renal disease in this treatment group was considered to be a contributing factor in the increased mortality.

A carcinogenic effect of tetrachloroethylene was not observed from pathologic examination of the animals. Statistical analysis of the data showed numerous non-neoplastic abnormalities which occurred spontaneously and were within the normal variation encountered in lifetime studies with this strain of rat. With respect to tumor findings, statistical analysis of the data did not reveal a definite increased tumor incidence in animals exposed to tetrachloroethylene. Tumor or tumor-like changes in the kidney were found in 1/189 control, 2/94 low-dose, and 4/94 high-dose males during gross necropsy; however, light microscopic examination of kidney lesions did not show a statistically significant tumor incidence compared to controls. Although many tumor types were found in treated and control animals, there was no statistically significant ($P > 0.05$) increase in tumor incidence at any anatomical site.

TABLE 8. CUMULATIVE SURVIVAL OF SPRAGUE-DAWLEY RATS EXPOSED TO TETRACHLOROETHYLENE FOR 12 MONTHS (adapted from Rampy et al. 1978)

Month of Study	0 ppm		300 ppm		600 ppm	
	Male	Female	Male	Female	Male	Female
Initial	189	189	94	91	94	94
6	187	188	94	91	88[a]	94
12	183	185	91	91	84[a]	91
18	155	151	74	77	55[a]	86[a]
24	44	70	26	37	13[a]	49[a]
31	1	12	1	6	1	5

[a] $p < 0.005$ by the Fisher Exact Test.

The results of this study do not indicate a definite carcinogenic effect of tetrachloroethylene in Sprague-Dawley rats, i.e., the tumor incidence between control and treated rats was similar. However, this study has the following drawbacks: 1) the period of exposure was only 12 months rather than over the lifetime of the animals, which would have been a more appropriate duration for carcinogenicity studies, and 2) the dose levels in this study do not appear to have been high enough to provide maximum sensitivity.

Intraperitoneal Administration Study (Theiss et al. 1977)

Theiss et al. (1977) tested tetrachloroethylene for carcinogenicity in the strain A mouse pulmonary tumor induction system. The test sample, a product of Aldrich Chemical Company, was reagent grade with a purity exceeding 95 to 99%. Strain A/St male mice, 6 to 8 weeks old, were used in this assay. The maximum tolerated dosage, defined as the dosage which five mice tolerated after six intraperitoneal injections over a 2-week period followed by a 4-week observation period, was determined and used in the bioassay. In the main test, 20 mice per treatment group received three intraperitoneal injections of 80, 200, or 400 mg/kg of tetrachloroethylene weekly until total dosages of 1120, 4800, and 9600 mg/kg, respectively, were achieved. Survivors were sacrificed at 24 weeks after the first injection, and the number of surface adenomas was counted. Results were compared with findings in vehicle (tricaprylin) and untreated controls by the Student t test. Tetrachloroethylene did not statistically increase ($P > 0.05$) the incidence of pulmonary tumors in this study (Table 9). This strain was sensitive to the positive control chemical urethan as shown in Table 9.

TABLE 9. PULMONARY TUMOR RESPONSE TO TETRACHLOROETHYLENE
(adapted from Theiss et al. 1977)

Compound	Dosage (mg/kg)	No. Survivors/ No. Animals	No. Lung Tumors/mouse
Tricaprylin	---	46/50	0.39 ± 0.06[a]
Tetrachloroethylene	80	15/20	0.27 ± 0.07
	200	17/20	0.41 ± 0.10
	400	18/20	0.50 ± 0.12
Urethan	1,000 mg/kg (1 injection)	20/20	19.6 ± 2.4

[a] Mean ± S. E.

A negative result in this assay is not considered conclusive, since several chemicals known to be carcinogenic in chronic rodent bioassays induce no response in this assay.

The strain A mouse pulmonary tumor assay is relatively insensitive to mouse carcinogens for which the effect is confined to the liver (Theiss et al. 1977).

For example, chloroform, 2-chloroethyl ether, and hexachlorocyclohexane induce tumors of the liver (not other sites) in mice (NCI 1976, 1977c, Innes et al. 1969) but were not carcinogenic in the assay by Theiss et al. (1977). The reasons for the negative lung response are not understood, but may be due to a smaller concentration of activating enzymes in the lung than the liver.

Skin Painting Study (Van Duuren et al. 1979)

A carcinogenicity study of purified tetrachloroethylene in ICR/Ha Swiss mice was described by Van Duuren et al. (1979). Maximum tolerated dosages were determined in range-finding studies, 6- to 8-weeks in duration, and were selected as dosages that did not affect body weight gain or produce clinical signs of toxicity. This study included the following experiments: 1) 30 females were treated topically on the dorsal skin with a single application of 163 mg tetrachloroethylene followed 14 days later by applications of 5.0 ug phorbol myristate acetate (PMA) to the skin three times weekly until termination of the study at 428 to 576 days; median survival time was 428 to 576 days. 2) 30 females were given thrice weekly topical applications of 54 mg tetrachloroethylene for the duration of the test (440 to 594 days) with a median survival time of 317 to 589 days. A vehicle (acetone) control group of 30 mice and an untreated control group of 100 mice were included in these experiments.

In the initiation-promotion experiment, 210 mice treated with PMA alone were also on test. The mice were 6- to 8-weeks old at the beginning of the study and were housed six to a cage. Test sites on the skin were shaved as necessary and were not covered; however, it was the authors' impression that tetrachloroethylene was immediately absorbed and that evaporation from test sites was minimal (written communication with B.L. Van Duuren, New York University). The animals were weighed monthly, and each animal was examined by necropsy. Tumors and lesions as well as skin, liver, stomach, and kidney were examined histologically.

Tetrachloroethylene did not show initiating activity in the initiation-promotion experiment; the number of mice with skin papillomas (squamous cell carcinomas) was: 4 (0) initiated with tetrachloroethylene, 15 (3) treated with PMA alone, and 0 (0) in the control groups. The study involving repeated application to the skin produced lung and stomach tumors in 16 and 0 tetrachloroethylene-treated mice, respectively; 11 and 2 vehicle-treated controls, respectively; and 30 and 5 untreated controls, respectively.

The negative results in mouse skin as an initiator and as a complete carcinogen can be reconciled with the positive mouse liver response in the NCI study if it is hypothesized that the skin does not have the necessary enzymes to convert tetrachloroethylene to an active metabolite, whereas, the liver does have this capability.

The insensitivity of skin application compared with other routes of exposure is apparent from the results of Van Duuren et al. (1979) with 1-chloroprene, _cis_-1,3-dichloropropene, and 2-chloropropenal. They found that more of the three compounds induced a response as initiators in initiation-promotion experiments or with repeated topical application on the skin. However, they did observe a statistically significant increase in the incidence of forestomach tumors in female Ha:ICR Swiss mice dosed by gavage with 1-chloroprene ($P < 0.0005$) and 2-chloropropenal ($P < 0.05$) and in the incidence of local sarcomas in female Ha:ICR Swiss mice treated with _cis_-1,3-dichloropropene ($P < 0.0005$) by subcutaneous injection.

EPIDEMIOLOGICAL STUDIES

There are three epidemiological studies in progress concerning tetrachloroethylene. In one, the National Institute for Occupational Safety and Health (NIOSH) has contracted for a retrospective cohort study of mortality of dry cleaning industry workers exposed to tetrachloroethylene for at least one year prior to 1960. The contract is monitored by the Biometry Section of the NIOSH Industry-Wide Studies Branch. The information presented here was taken from a 1980 report to NIOSH which has not been published in the open literature (Kaplan 1980).

The author reports that the levels of tetrachloroethylene are "much higher" for cleaners (machine operators) than for the other employees of the dry cleaning shops. A geometric mean time-weighted average for tetrachloroethylene was 22 ppm for the machine operators. For all other jobs, the highest corresponding value was given as 3.3 ppm. These data were provided through a NIOSH industrial hygiene survey of dry cleaning facilities.

The study cohort, selected from records maintained by several labor unions, consisted of 1,597 individuals employed more than 1 year prior to 1960 in dry cleaning establishments. The primary solvent was tetrachloroethylene. Efforts were made by the author to exclude all persons with previous occupational exposure to carbon tetrachloride or trichloroethylene. By the end of the study period 9/30/77, 1,058 were found alive, 285 deceased, and 254 were of unknown vital status. The extent of follow-up varied by sex; 8% of the males and 20.4% of the females remained lost to follow-up. Race was known only for the deceased based on death certificate data. Because of the lack of information regarding race, observed deaths by cause were compared to expected deaths derived via three separate methods: expected "white" deaths, expected "black" deaths, and a composite point estimate Standard Mortality Ratio (SMR) for both.

Based on the assumption that every member of the cohort was white, expected "white" deaths were derived by multiplying the person-years accumulated for the entire cohort by the white death rates within 5-year age groups (separately for males and females and then adding the two). "Black" expected deaths were similarly generated by assuming all cohort members were black. Composite expected deaths were calculated by weighting the total accumulated person-years for the cohort in each 5-year age group by the proportion of person-years attributable to the deceased blacks and the proportion attributable to deceased whites and then multiplying each total separately by the corresponding white and black death rates and finally adding to get the "composite" expected deaths. A SMR of 112 was calculated by dividing the total observed cancer deaths by the total expected cancer deaths. No significance tests were done by the author. None of the calculated SMR's were found to be statistically significant following closer examination by the CAG. The author called attention to the finding of 11 observed deaths from malignant neoplasms of the colon as possibly related to occupational exposure (6.98 white expected deaths, 6.77 black expected deaths, and composite SMR = 182). However, according to the CAG's calculations, this figure is not statistically significant. The author points out that confounding by socioeconomic status could have contributed to an underestimate of the risk of colon cancer.

No conclusion can be drawn from the study because of the incomplete follow-up, which was only 85% of the cohort population, the relatively short observation period of no more than 18 years, and the potential bias introduced by the author's failure to sufficiently control important confounding variables.

A second study (Blair et al. 1979), initiated by the NCI, involves a proportionate mortality study of laundry and dry cleaning workers who had been exposed to various solvents. Mortality statistics, obtained from historical dues records of two union locals in St. Louis, Missouri during the period 1957 to 1977, are being evaluated. The study is being conducted by the Environmental Epidemiology Branch of the NCI. Preliminary findings concerning the causes of death of 330 workers by the proportionate mortality method indicate an increased risk for malignant neoplasms within this occupational group. These findings are still current; however, the author is presently doing a historic prospective study of over 10,000 tetrachloroethylene-exposed dry cleaning workers (Blair 1981, personal communication).

Death certificates of 330 former members of two dry cleaning union locals were reviewed for cause of death and the distribution by cause of death was compared to that expected based on the proportionate mortality experience of the U.S. population. Cancers of the lung, cervix, uteri, and skin contributed to the excess cancer in this group of deaths. For lung cancer, there were 17 observed vs. 10 expected ($P < 0.05$), for cervix and uteri, 10 observed vs. 4.8 expected ($P < 0.05$), and for skin, 3 observed vs. 0.7 expected ($P < 0.05$). On the other hand, a significant deficit of deaths occurred in the cause "all circulatory diseases," with 100 observed vs. 125.9 expected ($P < 0.005$), which could account for the excess proportion of cancers.

The positive results should be regarded as only suggestive of a carcinogenic effect of tetrachloroethylene because of the limitations of the proportional mortality approach to characterizing cancer patterns and because the 330 deaths included in this study constitute only a nonrandom and possibly biased subset of total deaths among individuals even belonging to the two locals under study.

A third study is being conducted by Dr. Nabih Assad (personal communication, 1980) of Oklahoma University. This is a study of the death certificates of dry cleaning workers in Oklahoma. The preliminary results suggest increased death from kidney cancer in male workers of dry cleaning establishments in Oklahoma.

Details of this study are not yet available to assess its significance.

In summary, the results of these three epidemiological studies do not provide conclusive evidence that tetrachloroethylene is a human carcinogen due to the limitations inherent in each of the three studies.

VII. UNIT RISK ESTIMATE

In estimating risk to tetrachloroethylene from air exposure to humans, it would have been preferable to use an inhalation study showing positive results. However, only the gastric intubation study showed positive results; these were liver tumors in mice. The inhalation study performed in rats at less than the maximum tolerated dose produced negative results. The CAG calculated the upper-limit slope from the negative inhalation study and compared it with the estimated risk using the gastric intubation study with the result that the intubation study gives a risk of about 40 times higher than that using the upper-limit of risk from the negative inhalation study. The decision was made not to base the human risk estimate on the rat inhalation study, even though it represents a more appropriate route of administration, because rats might not be sensitive to the compound. The fundamental assumption is always made that humans are as sensitive as the most sensitive of animal species. The procedure and risk estimates from the intubation study in mice are shown below.

The NCI bioassay of tetrachloroethylene (1977b) showed that 32/49 (65%) and 27/48 (56%) of male mice had hepatocellular carcinomas of the liver after oral intubation of tetrachloroethylene at an average dose level of 536 and 1072 mg/kg/day, 5 days/week, for 78 weeks during the 90-week study period. The vehicle control male mice had a 10% (2/20) incidence rate of the same tumor type.

The lifetime average daily dose for the animals is

$$536 \times \frac{78}{90} \times \frac{5}{7} = 332 \text{ mg/kg/day}$$

The equivalent human lifetime dose is

$$332 \times \left(\frac{0.03}{70}\right)^{1/3} = 25.031 \text{ mg/kg/day}$$

assuming the average human body weight of 70 kg and the average male mouse body weight of 0.03 kg. The value $(0.03 \div 70)^{1/3}$ is a factor converting the effective dose from mice to humans, assuming that the amount of the direct-acting agent is proportional to the body surface area.

The unit risk calculation is based on the incidence of hepatocellular carcinoma in the male mice. The data from the highest dose group is excluded in fitting the multistage model due to the lack of fit, probably because of excess mortality.

The 95% upper confidence limit for the carcinogenic potency (slope) for the human is

$$q_1^* = 5.31 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$$

CALCULATION OF RISK

To estimate the risk corresponding to 1 ug/m^3 tetrachloroethylene concentration in the ambient air, the effective dose expressed in mg/kg/day must be estimated first.

Assuming that the average air intake for a 70 kg man is 20 m^3/day, the total tetrachloroethylene intake by an individual would be

$$10^{-3} \text{ mg/m}^3 \times 20 \text{ m}^3\text{/day} \div 70 \text{ kg} = 2.86 \times 10^{-4} \text{ mg/kg/day}$$

Assuming that 50% of tetrachloroethylene inhaled is absorbed into the body system, and based on two human acute inhalation studies (Bolanowska and Golacka 1972, Fernandez et al. 1976), the effective dose would be

$$\begin{aligned} d &= 2.86 \times 10^{-4} \times 0.50 \\ &= 1.43 \times 10^{-4} \text{ mg/kg/day} \end{aligned}$$

The risk corresponding to d is

$$P = 1 - \exp[-5.31 \times 10^{-2} \times 1.43 \times 10^{-4}]$$
$$= 7.59 \times 10^{-6}$$

For drinking water ingestion of 2 liters per day throughout life, the average daily dose, assuming a tetrachloroethylene concentration of 1, ug/l is

$$d = 2\ \text{l/day} \times 10^{-3}\ \text{mg/l} \times 1/(70\ \text{kg})$$
$$= 2.86 \times 10^{-5}\ \text{mg/kg/day}$$

The upper-limit risk corresponding to this concentration is

$$P = 1 - \exp\ [-5.31 \times 10^{-2} \times 2.86 \times 10^{-5}]$$
$$= 1.5 \times 10^{-6}$$

In this calculation the linearized multistage model is used to give an estimate of a plausible upper-bound of lifetime cancer risk, recognizing that uncertainties in the extrapolation process may give rise to a lower-bound of zero risk. Using this procedure, the plausible range of the unit risk estimate is from zero to 7.6 x 10^{-6} for a person continuously exposed to 1 ug of tetrachloroethylene per cubic meter of air. However, in view of the inconclusive nature of the presently available evidence for the mutagenicity of tetrachloroethylene, the upper-bound of risk is presently regarded as having limited plausibility.

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